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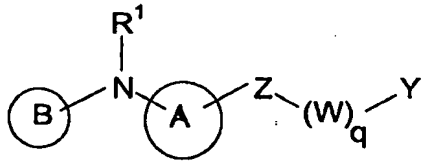
(54) Title: CHEMICAL COMPOUNDS

(57) Abstract

Compound of formula (I) wherein: A is a bicyclic heteroaryl, optionally substituted with one or more substituents; B is aryl or a mono or bicyclic heteroaryl, each of which can be optionally subsituted with one or more subsituents; Z is $-X(CR^aR^b)_aCO$, –NH, –CO or the group $X-(CH_2)_bCONH\ (CH_2)_cNH$ where X is oxygen, sulphur, amino, alkylamino or a direct bond, R^a and R^b are independently hydrogen or C_{1-4} alkyl, a is an integer from 1 to 4, b is 1 or 2 and c is from 2 to 5, and; W is $-NHCH(R^w)CO-$ or $OC(R^w)CHNH$ where R^w is $-CH_2CH(CH_3)_2-CH_2CH_2S(CH_3)$ or $CH_2CH_2S(O_2)(CH_3)$; q is 0 or 1 and when q is 0 Z is linked to the group W by the formation of an amide bond between Z and Y, and when q is 1 Z is linked to the group W by the formation of an amide bond between Z and W and W is linked to the group Y by the formation of an amide bond between W and Y; Y is a fragment derived from the C–terminus of a compound which inhibits the interaction between the integrin $\alpha_{IIb}\beta_3$ and its ligand fibrinogen; R^1 is hydrogen, C_{1-5}alkyl, C_{1-3} alkanoyl or C_{1-3} alkoxycarbonyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable derivative thereof.



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CHEMICAL COMPOUNDS

This invention relates to compounds which are inhibitors of the interaction between the integrin $\alpha_4\beta_1$, also known as Very Late Antigen-4 (VLA-4) or CD49d/CD29, and its protein ligands, for example Vascular Cell Adhesion Molecule-1 (VCAM-1) and fibronectin. This invention further relates to processes for preparing such compounds, to pharmaceutical compositions containing them and to their use in methods of therapeutic application.

$\alpha_4\beta_1$ is a member of the integrin family of heterodimeric cell surface receptors that are composed of noncovalently associated glycoprotein subunits (α and β) and are involved in cell adhesion to other cells or to extracellular matrix. There are at least 14 different human integrin α subunits and at least 8 different β subunits and each β subunit can form a heterodimer with one or more α subunits. Integrins can be subdivided based on their β subunit composition. $\alpha_4\beta_1$ is one of several β_1 integrins, also known as Very Late Antigens (VLA).

The interactions between integrins and their protein ligands are fundamental for maintaining cell function, for example by tethering cells at a particular location, facilitating cell migration, or providing survival signals to cells from their environment. Ligands recognised by integrins include extracellular matrix proteins, such as collagen and fibronectin; plasma proteins, such as fibrinogen; and cell surface molecules, such as transmembrane proteins of the immunoglobulin superfamily and cell-bound complement. The specificity of the interaction between integrin and ligand is governed by the α and β subunit composition.

Integrin $\alpha_4\beta_1$ is expressed on numerous hematopoietic cells and established cell lines, including hematopoietic precursors, peripheral and cytotoxic T lymphocytes, B lymphocytes, monocytes, thymocytes and eosinophils [Hemler, M.E. et al (1987), J. Biol. Chem., 262, 11478-11485; Bochner, B.S. et al (1991), J. Exp. Med., 173, 1553-1556]. Unlike other β_1 integrins that bind only to cell-extracellular matrix proteins, $\alpha_4\beta_1$ binds to VCAM-1, an immunoglobulin superfamily member expressed on the cell surface, for example on vascular endothelial cells, and to fibronectin containing the alternatively spliced type III connecting segment (CS-1 fibronectin) [Elices, M.J. et al (1990), Cell, 60, 577-584; Wayner, E.A. et al (1989). J. Cell Biol., 109, 1321-1330].

The activation and extravasation of blood leukocytes plays a major role in the development and progression of inflammatory diseases. Cell adhesion to the vascular endothelium is required before cells migrate from the blood into inflamed tissue and is mediated by specific interactions between cell adhesion molecules on the surface of vascular endothelial cells and circulating leukocytes [Sharar, S.R. et al (1995). Springer Semin. Immunopathol., 16, 359-378]. $\alpha_4\beta_1$ is believed to have an important role in the recruitment of lymphocytes, monocytes and eosinophils during inflammation. $\alpha_4\beta_1$ /ligand binding has also been implicated in T-cell proliferation, B-cell localisation to germinal centres, haemopoeitic progenitor cell localisation in the bone marrow, placental development, muscle development and tumour cell metastasis.

The affinity of $\alpha_4\beta_1$ for its ligands is normally low but chemokines expressed by inflamed vascular endothelium act via receptors on the leukocyte surface to upregulate $\alpha_4\beta_1$ function [Weber, C. et al (1996), J. Cell Biol., 134, 1063-1073]. VCAM-1 expression is upregulated on endothelial cells *in vitro* by inflammatory cytokines [Osborn, L. et al (1989) Cell, 59, 1203-1211] and in human inflammatory diseases such as rheumatoid arthritis [Morales-Ducret, J. et al (1992). J. Immunol., 149, 1424-1431], multiple sclerosis [Cannella, B. et al., (1995). Ann. Neurol., 37, 424-435], allergic asthma [Fukuda, T. et al (1996), Am. J. Respir. Cell Mol. Biol., 14, 84-94] and atherosclerosis [O'Brien, K.D. et al (1993). J. Clin. Invest., 92, 945-951].

Monoclonal antibodies directed against the α_4 integrin subunit have been shown to be effective in a number of animal models of human inflammatory diseases including multiple sclerosis, rheumatoid arthritis, allergic asthma, contact dermatitis, transplant rejection, insulin-dependent diabetes, inflammatory bowel disease, and glomerulonephritis.

Integrins recognise short peptide motifs in their ligands The minimal $\alpha_4\beta_1$ binding epitope in CS-1 is the tripeptide leucine-aspartic acid-valine (Leu-Asp-Val) [Komoriya, A., et al (1991). J. Biol. Chem., 266, 15075-15079] while VCAM-1 contains the similar sequence isoleucine-aspartic acid-serine [Clements, J.M., et al (1994). J. Cell Sci., 107, 2127-2135]. The 25-amino acid fibronectin fragment, CS-1 peptide, which contains the Leu Asp-Val motif, is a competitive inhibitor of $\alpha_4\beta_1$ binding to VCAM-1 [Makarem, R., et al (1994). J. Biol. Chem., 269, 4005-4011]. Small molecule $\alpha_4\beta_1$ inhibitors based on the Leu-Asp-Val sequence in CS-1 have been described, for example the linear molecule phenylacetic

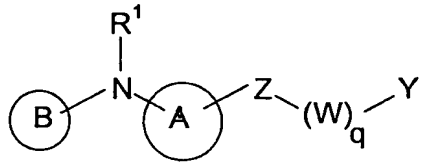
acid-Leu-Asp-Phe-D-Pro-amide [Molossi, S. et al (1995). J. Clin. Invest., 95, 2601-2610] and the disulphide cyclic peptide Cys-Trp-Leu-Asp-Val-Cys [Vanderslice, P., et al (1997). J. Immunol., 158, 1710-1718].

More recently, non- and semi-peptidic compounds which inhibit $\alpha_4\beta_1$/VCAM binding and which can be orally administered have been reported in for example, WO96/22966 and WO98/04247.

There remains a continuing need for alternative compounds which inhibit the interaction between VCAM-1 and fibronectin with integrin $\alpha_4\beta_1$ and, in particular, for compounds which can be administered by an oral route.

We have now found a group of compounds which contain a bicyclic heteroaryl ring system which inhibit this interaction.

Accordingly the present invention provides a compound of formula (I)



(I)

wherein:

A is a bicyclic heteroaryl, optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, halogeno, nitro, cyano, amino trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to the nitrogen via a ring carbon atom in one ring and to the group Z by a ring carbon atom in the second ring;

B is aryl or a mono or bicyclic heteroaryl, each of which can be optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6}

$_6$)alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, phenoxy, cyano, nitro, amino, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to NR^1 through a ring carbon atom;

Z is -$X(CR^aR^b)_aCO$, -NH, -CO or the group -X-$(CH_2)_bCONH(CH_2)_cNH$ where X is oxygen, sulphur, amino, alkylamino or a direct bond, R^a and R^b are independently hydrogen or C_{1-4} alkyl, a is an integer from 1 to 4, b is 1 or 2 and c is from 2 to 5, and;

W is -$NHCH(R^w)CO$- or $OC(R^w)CHNH$ where R^w is -$CH_2CH(CH_3)_2$ -$CH_2CH_2S(CH_3)$ or $CH_2CH_2S(O_2)(CH_3)$;

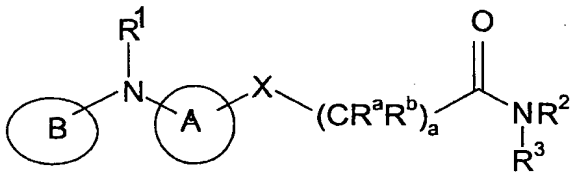
q is 0 or 1 and when q is 0 Z is linked to the group Y by the formation of an amide bond between Z and Y, and when q is 1 Z is linked to the group W by the formation of an amide bond between Z and W and W is linked to the group Y by the formation of an amide bond between W and Y;

Y is a fragment derived from the C-terminus of a compound which inhibits the interaction between the integrin $\alpha_{IIb}\beta_3$ and its ligand fibrinogen;

R^1 is hydrogen, C_{1-5} alkyl, C_{1-3} alkanoyl or C_{1-3} alkoxycarbonyl;

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

In one aspect of the invention the compound has the formula (II)



(II)

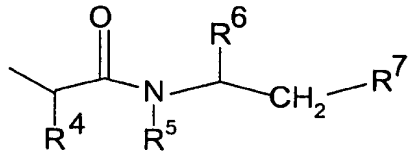
wherein:

A, B, R^a, R^b and 'a' are as hereinbefore defined;

X is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

R^3 is hydrogen or C_{1-5} alkyl;

R^2 is selected from a group of formula (III) or (IV),



(III)

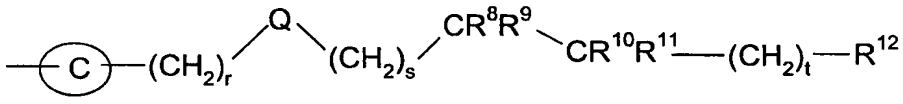
where

R^4 is selected from C_{1-6} alkyl, C_{1-6}alkoxy(C_{1-6})alkyl, C_{1-6}alkylS(C_{1-6})alkyl and C_{1-6}alkylS(O_2)(C_{1-6})alkyl;

R^5 is hydrogen or C_{1-5} alkyl;

R^6 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, and aryl optionally substituted by at least one substituent selected from C_{1-4} alkoxy, C_{1-6} alkyl, cyano, halogeno, and trifluoromethyl; and

R^7 is an acidic functional group;



(IV)

where

C is aryl, a monocyclic heteroaryl linked through ring carbon atoms, a bicyclic heteroaryl linked to nitrogen by a ring carbon in one ring and to the group $(CH_2)_r$ or, where r is zero, Q by a ring carbon in the second ring, the aryl and mono and bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl; and a substituent of formula (V)

$$U - (CH_2)_d - V - T \qquad (V)$$

wherein U is selected from oxygen, sulphur, a direct bond or -CH_2O-, V is selected from nitrogen, oxygen, sulphur or a direct bond, d is zero or a number from 1 to 4, and T is selected from R^c or, when V is nitrogen, R^cR^d, where R^c and R^d are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy(C_{1-6})alkyl or aryl; or a heterocycle

containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, optionally substituted with one or more substituents selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-4} alkylsulphonyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl, and linked to V through a ring carbon or nitrogen and with the proviso that when T is a heterocycle linked to V through a ring nitrogen then V is a direct bond;

Q is selected from a direct bond, methylene, oxygen, carbonyl, -C(OH)(H)- or Q together with the group $(CH_2)_s$ or CR^8R^9, when s is zero, form a C_2 alkenyl or C_2 alkynyl;

R^8 to R^{10} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heterocycle, the aryl and heterocycle optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{1-4}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl, or two of R^8 to R^{10} can be taken together to form phenyl or a 3-7 membered heterocycle;

R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, hydroxy, amido, heterocycle and aryl, the heterocycle, and aryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{1-4}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{12} is an acidic functional group;

r is zero or 1;

s is zero, 1 or 2;

t is zero or a number from 1 to 3;

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

In this specification the following definitions are adopted:-

'Bicyclic heteroaryl' means an aromatic 5,6- 6,5- or 6,6- fused ring system wherein one or both rings contain ring heteroatoms. The ring system may contain up to three

heteroatoms, independently selected from oxygen, nitrogen or sulphur and can be optionally substituted with one or more substituents selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-4} alkylsulphonyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl. When the ring system contains more than one heteratom at least one heteroatom is nitrogen. Examples of bicyclic heteroaryl's include quinazolinyl, benzothiophenyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, indolyl, quinolinyl, phthalazinyl and benzotriazolyl.

The term 'heterocycle' means an aromatic or non-aromatic saturated or partially saturated cyclic ring system containing up to five heteroatoms independently selected from nitrogen, oxygen and sulphur and which can be optionally substituted with one or more substituents selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-4} alkylsulphonyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl. Examples include 3 to 10 membered monocyclic or bicyclic rings with up to five heteroatoms selected from oxygen, nitrogen and sulphur, such as, for example, furanyl, pyrrolinyl, piperidinyl, piperazinyl, thienyl, pyridyl, imidazolyl, tetrazolyl, thiazolyl, pyrazolyl, pyrimidinyl, triazinyl, pyridazinyl, pyrazinyl, morpholinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl and tetrahydropyrimidinyl. The monocyclic heteroaryl is a aromatic ring system containing up to four heteroatoms, examples of which are given above.

'Aryl' typically means phenyl or naphthyl, preferably phenyl.

The 5 to 7 membered ring formed by substituents on ring B or substituents R^{13}, see below, can be an, optionally substituted, saturated or unsaturated ring with up to three heteroatoms independently selected from nitrogen, oxygen and sulphur.

The term 'acidic functional group' means a group which incorporates an acidic hydrogen and includes carboxylic acids, tetrazoles, acyl sulphonamides, sulphonic and sulphinic acids, and preferably is carboxy.

The term 'ester group' is an ester derived from a C_{1-10} straight or branched alkyl, arylalkyl or C_{5-7} cycloalkyl (optionally substituted with C_{1-4} alkyl) alcohol. Suitable ester groups are those of formula -COOR'' where R'' can be tert-butyl, 2,4-dimethyl-pent-3-yl, 4-methyl-tetrahydropyran-4-yl, 2,2-dimethyl aminoethyl or 2-methyl 3-phenyl prop-2-yl.

In this specification suitable specific groups for the substituents mentioned include:-

for halogeno:	fluoro, chloro, bromo and iodo
for C_{1-6}alkyl (this includes straight chained, branched structures and ring systems):	methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropane and cyclohexane;
for C_{2-6}alkenyl:	vinyl, allyl and but-2-enyl;
for C_{1-6}alkanoyl;	formyl, acetyl, propionyl or butyryl;
for C_{2-6}alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for C_{1-6}alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for C_{2-6}alkenyloxy:	vinyloxy and allyloxy;
for C_{2-6}alkynyloxy:	ethynyloxy and 2-propynyloxy;
for C_{1-6}alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-C_{1-6}alkylamino:	dimethylamino, diethylamino;
for C_{2-6}alkanoylamino:	acetamido, propionamido and butyramido;
for N-C_{1-6}alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for C_{1-6}alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for C_{1-4}alkoxyC_{1-6}alkyl:	methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl;
for C_{1-6} alkylthio:	methylthio;
for C_{1-4} alkylsulphonyl:	methylsulphonyl;
for C_{1-6}alkylaminoC_{1-6}alkyl:	$-CH_2NHC_2H_5$

Y is derived from a compound which inhibits the interaction between the integrin $\alpha_{IIb}\beta_3$ and its ligand fibrinogen. Compounds which inhibit this interaction comprise a component containing an acid functional group that mimics the acidic amino acid-containing sequence in fibrinogen that is recognised by $\alpha_{IIb}\beta_3$. $\alpha_{IIb}\beta_3$ antagonists would be expected to inhibit fibrinogen binding to platelets and platelet aggregation in vitro. Methods that can be used to look at such inhibition are described in, for example, S A Mousa et al., Therapy and Prevention, (October 1996), 7(10), 767-774; T Aoki et al., Thrombosis Research (1996), 81 (4), 439-450; and B D Guth et al., and J Cardiovascular Pharmacology, (1997), 30, 261-272. Suitable compounds are described in the following patents/applications which are incorporated herein by reference: EP 608759 (Merck), WO95/18111 (Du Pont Merck), DE 4 241 632 (Thomae), EP 655 439 (Lilly), EP 540334 (Merck), US 5 334 596 (Merck), WO94/12181 (Merck), WO 94/18981 (Merck), DE 4405633 (Merck), EP 645376 (Merck), WO93/07867 (Monsanto), US 5 344 957 (Monsanto), US 5 314 902 (Monsanto), WO94/22820 (Searle), EP587134 (Thomae), EP503548 (Thomae), EP542363 (Glaxo), WO93/14077 (Glaxo), WO95/18619 (SmithKline Beecham), EP632020 (Zeneca), EP727425 (Merck), WO94/08962(Merck), EP560730 (Sandoz), EP505868 (Hoffmann), EP381033 (Hoffman-La Roche), EP529858 (Takeda), WO94/12478 (Smith Kline Beecham), WO93/00095 (Smith Kline Beecham), WO94/29273 (Smith Kline Beecham), WO95/25091 (Ortho), EP632016 (Zeneca), WO96/22288 (Eli Lilly) and WO96/29309 (Fujisawa). Other suitable compounds are disclosed in S A Mousa et al., (1997), Drug Discovery Today, 2 (5), 187-199.

It is to be understood that, insofar as certain of the compounds of the formula (I), (II), (VI), (VIII) and (IX) defined above and below may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which can inhi bit the interaction between VCAM-1 and fibronectin with the integrin $\alpha_4\beta_1$. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

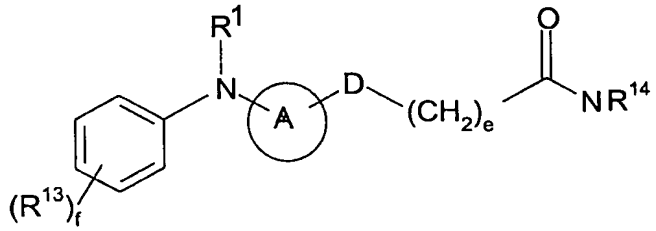
According to a further aspect of the invention in the compound of formula (I),

R^1, A, Z, W, q and Y are as hereinbefore defined;

B is a phenyl optionally substituted with up to five substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, are - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form a 5-7 membered ring; and when Z is -X-$(R^aR^b)_aCO$- then R^a and R^b are both hydrogen

or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof.

In a further aspect of the invention the compound has the formula (VI)



(VI)

wherein:

A, and R^1 are as hereinbefore defined;

each R^{13} is independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form a 5-7 membered ring;

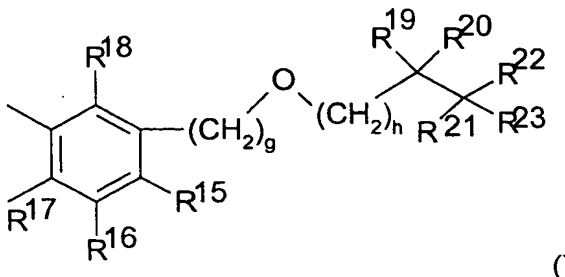
D is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

e is an integer from 1 to 4;

f is zero or an integer from 1 to 5;

R^{14} is selected from a group of formula (III), as hereinbefore defined where R^4 is C_{1-6} alkyl, C_{1-6}alkoxy(C_{1-6})alkyl, and C_{1-6}alkylS(C_{1-6})alkyl;

or from a group of formula (VII)



(VII)

where

R^{15} to R^{18} are each independently hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2 - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

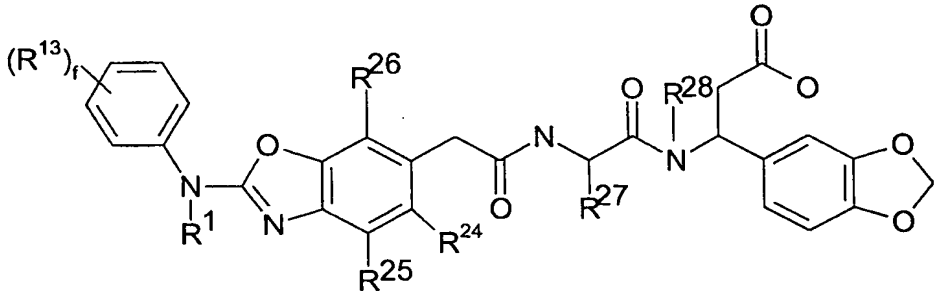
R^{19} to R^{22} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heteroaryl containing up to 2 heteroatoms chosen from oxygen, sulphur and nitrogen, the aryl and heteroaryl optionally substituted with one or more substituents selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6}, or two of R^{19} to R^{22} can be taken together to form phenyl or 3 to 7 membered heterocycle;

R^{23} is an acidic functional group; and

g and h are each independently 0 or 1;

or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof.

In another aspect of the invention the compound is of formula (VIII)



(VIII)

wherein:

R^1, R^{13} and f are as hereinbefore defined;

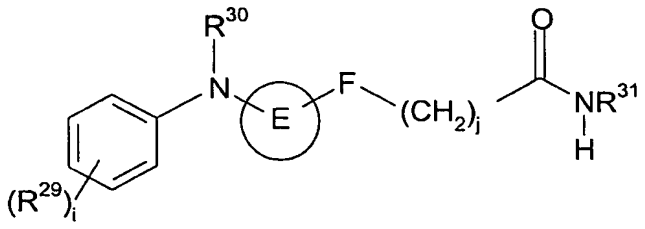
R^{24} to R^{26} are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkanoyl or halogeno;

R^{27} is $-CH_2CH(CH_3)(CH_3)$ or $-CH_2CH_2SCH_3$; and

R^{28} is hydrogen or C_{1-5} alkyl;

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

In yet a further aspect of the invention, the compound is of formula (IX)



(IX)

wherein:

each R^{29} is independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form phenyl or a 5-7 membered heterocycle;

R^{30} is hydrogen, C_1-$_5$ alkyl, C_1-$_3$ alkanoyl or C_1-$_3$ alkoxycarbonyl;

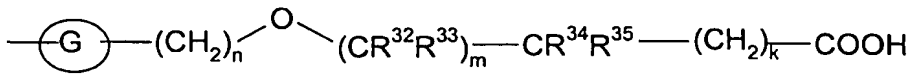
E is a bicyclic heteroaryl optionally substituted with one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkanoyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, halogeno, nitro, cyano, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, and is linked to the nitrogen via a ring carbon atom in one ring and to the group F by a ring carbon atom in the second ring;

F is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

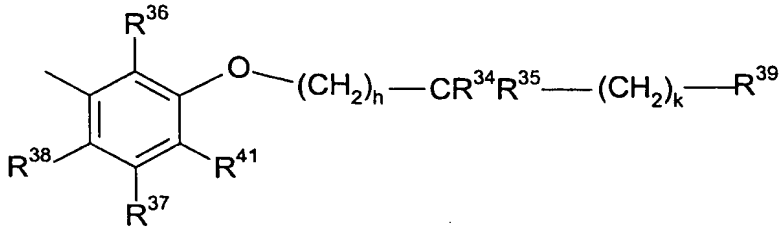
i is zero or an integer from 1 to 4;

j is an integer from 1 to 4;

R^{31} is selected from a group of formula (X) or (XI)



(X)



(XI)

where

R^{41} is a group of formula U - $(CH_2)_d$ - V -T as hereinbefore defined:

G is aryl, a monocyclic heteroaryl linked through ring carbon atoms, a bicyclic heteroaryl linked to nitrogen by a ring carbon in one ring and to the group $(CH_2)_n$ or oxygen by a ring carbon in the second ring, the aryl and mono and bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{32} to R^{34} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heterocycle, the aryl and heterocycle optionally substituted with one or more substituents independently selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, -CO_2R^e and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl or two of R^{32} to R^{34} can be taken together to form phenyl or a 3-7 membered heterocycle;

R^{35} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, amido, heterocycle and aryl, the heterocycle, and aryl optionally substituted with one or more substituents independently selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano,

halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, $-CO_2R^e$ and $-CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{36} to R^{38} are each independently hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2 - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{39} is an acidic functional group;

h and n are zero or 1;

m is zero, 1 or 2;

k is zero or a number from 1 to 3;

or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof.

Particularly suitable compounds or pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof are those defined below:-

A) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as hereinbefore defined, for example, C_{1-4} alkoxy, halogeno, alkylthio and alkylsulphonyl, and especially where R^{40} is a C_{1-4} alkoxyl, for example methoxy, B is phenyl, optionally substituted as hereinbefore defined, but preferably phenyl, A and B are linked together as shown in figure (1),

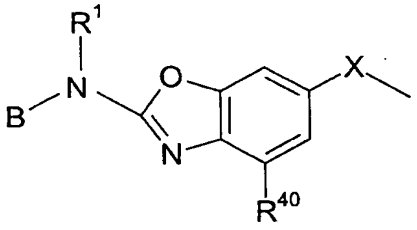


figure (1)

X is a direct bond or oxygen, preferably a direct bond, R^1 is hydrogen or C_{1-2} alkyl, preferably hydrogen and

(i) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, C_{1-6}alkylS(C_{1-6})alkyl or C_{1-6}alkylS(O_2)(C_{1-6})alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl, R^7 is carboxy;

(ii) R^3 is methyl, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(iii) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, C_{1-6}alkylS(C_{1-6})alkyl or C_{1-6}alkylS(O_2)(C_{1-6})alkyl, R^5 is hydrogen, R^6 is C_{1-6} alkyl and R^7 is carboxy;

(iv) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is -COOR", where R" is 2,4-dimethyl-pent-3-yl or 2,2-dimethylaminoethyl, isopropoxyphenyl; $-C_2H_4N(CH_3)_2$ and R^7 is carboxy;

(v) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as hereinbefore defined, and preferably R^8 to R^{11} are all hydrogen or R^8 to R^{10} are all hydrogen and R^{11} is C_{1-4} alkyl, hydroxy or phenyl optionally substituted with C_{1-4} alkyl ;

(vi) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl substituted with one or more substituents selected from methoxy, cyano, halogeno, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as hereinbefore defined and preferably R^8 to R^{10} are all hydrogen and R^{11} is C_{1-4} alkyl;

(vii) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl or a C_{2-3} alkenyl, preferably 1,3-benzodioxol-5-yl, R^{12} is carboxy, r and s are both zero and t is 1;

(viii) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl substituted with a C_{1-4} alkoxy, C_{1-4} alkyl, halogeno, or trifluoromethyl, preferably C_{1-4} alkoxy, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl or a C_2 alkenyl, preferably 1,3-benzodioxol-5-yl, R^{12} is carboxy, r and s are both zero and t is 1;

(ix) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl optionally substituted with C_{1-4} alkoxyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is a nitrogen containing heterocycle, preferably piperidinyl or morpholinyl, R^{12} is carboxy, r and s are both zero and t is 1;

(x) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl, optionally substituted with C_{1-4} alkoxyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is phenyl substituted with a C_3 alkoxy, R^{12} is carboxy, r and s are both zero and t is 1;

(xi) R^3 is methyl and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as hereinbefore defined, and

preferably R^8 to R^{11} are all hydrogen or R^8 to R^{10} are all hydrogen and R^{11} is C_{1-4} alkyl, hydroxy or phenyl optionally substituted with C_{1-4} alkyl; or

(xii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r is zero, s and t are both one and R^8 to R^{11} are all hydrogen

B) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as hereinbefore and especially where R^{40} is a C_{1-4} alkoxyl, for example methoxy, and B is phenyl, optionally substituted as hereinbefore defined, but preferably phenyl, A and B are linked together as shown in figure (2)

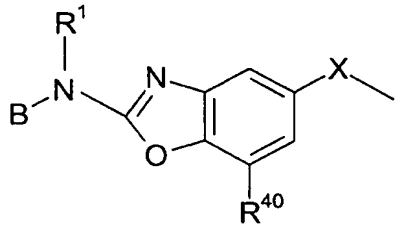


figure (2)

X is a direct bond and R^1 is hydrogen or C_{1-2} alkyl and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as hereinbefore defined, preferably R^8 to R^{11} are all hydrogen.

C) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzimidazolyl, optionally substituted as hereinbefore defined, B is phenyl, optionally substituted as hereinbefore defined, X is a direct bond and R^1 is hydrogen or C_{1-2} alkyl; and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy or

(ii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as hereinbefore defined, preferably R^8 to R^{11} are all hydrogen.

D) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as hereinbefore defined especially where R^{40} is C_{1-4} methoxy, B is phenyl, optionally substituted as hereinbefore defined, but preferably phenyl, A and B are linked together as shown in figure (1), R^1 is hydrogen or C_{1-2} alkyl, X is a direct

bond or oxygen, preferably a direct bond, R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, r and s are both zero

i) R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl, R^{12} is carboxy, t is 1 and Q is -C(OH)(H)-, carbonyl, methylene;

ii) R^{11} is 1,3-benzodioxol-5-yl, R^{12} is carboxy, t is 1 and Q together with the group CR^8R^9 form a C_2 alkenyl or C_2 alkynyl; or

iii) R^{11} is hydrogen, R^{12} is carboxy, t is 1 and Q together with the group CR^8R^9 form a C_2 alkenyl or C_2 alkynyl.

E) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as hereinbefore defined and especially where R^{40} is a C_{1-4} alkoxyl, for example methoxy, B is naphthyl, pyridyl or N-oxidopyridyl optionally substituted as hereinbefore defined, A and B are linked together as shown in figure (1) above, X is a direct bond or oxygen, preferably a direct bond,and R^1 is hydrogen or C_{1-2} alkyl; and

(i) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen, and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as hereinbefore defined, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are all hydrogen.

F) Compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzothiazolyl, optionally substituted as hereinbefore defined, B is phenyl or pyridyl both optionally substituted as hereinbefore defined, A and B are linked together as shown in figure (3)

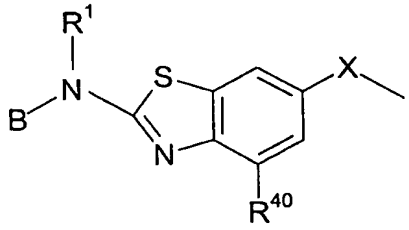


figure (3)

X is a direct bond or oxygen, preferably a direct bond, and R^1 is hydrogen or C_{1-2} alkyl, and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen, and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as hereinbefore defined, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are all hydrogen.

G) Compounds of formula (IX) where E is benzoxazolyl, optionally substituted as hereinforefore defined and especially where R^{40} is a C_{1-4} alkoxyl, for example methoxy, i is zero or 1, and is linked to the phenyl as shown in figure (1), F is a direct bond or oxygen, preferably a direct bond, R^{30} is hydrogen or C_{1-2} alkyl, preferably hydrogen, j is 1, R^{31} is a group of formula (XI), where R^{36} to R^{37} are as hereinbefore defined and preferably are all hydrogen, R^{39} is carboxy; and

i) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group C_{1-4}alkoxyC_{1-4}alkoxyl, preferably 2-methoxyethoxy,

ii) h and k are both 1, R^{34} and R^{35} are both hydrogen, R^{41} is the group O-$(CH_2)_d$-T where d is from 1 to 4, preferably 2 or 3, and T is a nitrogen containing heterocycle linked to oxygen through a ring nitrogen or ring carbon and preferably is selected from piperidinyl, morpholinyl, piperazinyl, methylpiperazinyl, pyrrolidinyl, imidazolyl and pyridyl;

iii) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group -O-$(CH_2)_d$-N-R^cR^d, where d is 2 or 3, R^c and R^d are each independently $(CH_2)_2OCH_3$, C_{1-4} alkyl or hydrogen;

iv) h and k are both 1, R^{34} is hydrogen, R^{35} is a C_{1-4} alkyl, preferably methyl, or 1,3-benzodioxol-5-yl, and R^{41} is the group -O-$(CH_2)_d$-T where d is from 1 to 4, preferably 2 or 3 and T is a nitrogen containing heterocycle linked to oxygen through a ring nitrogen and preferably is selected from piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl and pyridyl; or

v) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group -$(CH_2)_d$-T where d is 1 and T is morpholinyl.

H) Compounds of formula (II) a is 1, A is benzoxazolyl, optionally substituted as hereinbefore defined and especially where R^{40} is a C_{1-4} alkoxyl, for example methoxy, B is phenyl, optionally substituted as hereinbefore defined, but preferably phenyl, A and B are linked together as shown in figure (1) above, X is a direct bond and R^1 is hydrogen and

i) one or both of R^a and R^b are methyl, R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as hereinbefore defined, r and s are both zero, Q is oxygen, R^8 to R^{11} are hydrogen, t is 1 and R^{12} is carboxy; or

ii) one or both of R^a and R^b are methyl, R^3 is hydrogen and R^2 is a group of formula (III) where R^4 is a C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy.

A particular advantage of compounds of formula (IX), where R^{31} is a group of formula (XII), is that they show reduced non specific protein binding.

Particularly suitable compounds are those described in the Examples and in Table 1. Pharmaceutically acceptable salts include acid addition salts such as salts formed with mineral acids, for example, hydrogen halides such as hydrogen chloride and hydrogen bromide, sulphonic and phosphonic acids; and salts formed with organic acids, especially citric, maleic, acetic, oxalic, tartaric, mandelic, p-toluenesulphonic, methanesulphonic acids and the like. In another aspect, suitable salts are base salts such as alkali metals salts, for example, sodium and potassium; alkaline earth metal salts such as magnesium and calcium; aluminium and ammonium salts; and salts with organic bases such as ethanolamine, methylamine, diethylamine, isopropylamine, trimethylamine and the like. Such salts may be prepared by any suitable method known in the art.

In vivo hydrolysable derivatives include, in particular, pharmaceutically acceptable derivatives that may be oxidised or reduced in the human body to produce the parent compound or esters that hydrolyse in hte human body to produce the parent compound. Such esters can be identified by administering, for example, intravenously to the test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for hydroxy include acetyl and for carboxyl include, for example, alkyl esters, dialkylaminoalkoxy esters, esters of formula $-C(O)-O-CH_2C(O)NR^{a''}R^{b''}$ where $R^{a''}$ and $R^{b''}$ are, for example, selected from hydrogen and C_{1-4} alkyl, and C_{1-6}alkoxy methyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8} cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl.

The activities of the compounds of this invention to inhibit the interaction between VCAM-1 and fibronectin with integrin $\alpha_4\beta_1$ may be determined using a number of in vitro and in vivo screens.

For example, compounds of formulae (I), (II), (VI), (VIII) and (IX) preferably have an IC_{50} of <10μM, more preferably <1μM in the MOLT-4 cell/Fibronectin assay hereinafter described.

In order for it to be used, a compound of formulae (I), (II), (VI), (VIII) and (IX) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof is typically formulated as a pharmaceutical composition in accordance with standard pharmaceutical practice.

Thus, according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formulae (I), (II), (VI), (VIII) and (IX)or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension, or a depot formulation with drug incorporated in a biodegradable polymer. The composition may be in a form suitable for topical administration such as for example creams, ointments and gels. Skin patches are also contemplated. For these purposes, the compositions of this invention may be formulated by means known in the art, such as for example, as described in general terms, in Chapter 25.2 of Comprehensive Medicinal Chemistry, Volume 5, Editor Hansch et al, Pergamon Press 1990.

Furthermore, the pharmaceutical composition of the present invention may contain one or more additional pharmacological agents suitable for treating one or more disease conditions referred to hereinabove, in addition to the compounds of the present invention. In a further aspect, the additional pharmacological agent or agents may be co-administered, either simultaneously or sequentially, with the pharmaceutical compositions of the invention.

The composition of the invention will normally be administered to humans such that the daily dose will be 0.01 to 75mg/kg body weight and preferably 0.1 to 15mg/kg body weight. A preferred composition of the invention is one suitable for oral administration in

unit dosage form for example a tablet or capsule which contains from 1 to 1000mg and preferably 10 to 500mg of a compound according to the present invention in each unit dose.

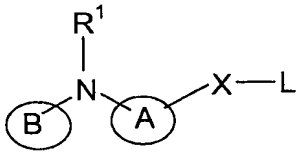
Thus, according to yet another aspect of the invention, there is provided a compound of formulae (I), (II), (VI), (VIII) and (IX) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect of the invention the present invention provides a method of treating a disease mediated by the interaction between VCAM-1 and/or fibronectin and the integrin receptor $\alpha_4\beta_1$ in need of such treatment which comprises administering to said warm-blooded mammals an effective amount of a compound of formulae (I), (II), (VI), (VIII) and (IX) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof.

The present invention also provides the use of a compound of formulae (I), (II), (VI), (VIII) and (IX) or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof in the production of a medicament for use in the treatment of a disease or medical condition mediated by the interaction between fibronectin and/or VCAM-1 (especially VCAM-1) and the integrin receptor $\alpha_4\beta_1$.

In a preferred embodiment the mammal in need of treatment is suffering from multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease, psoriasis, atherosclerosis, transplant rejection, inflammatory bowel disease, insulin-dependent diabetes and glomerulonephritis.

In another aspect of the invention, there is provided a process for preparing a compound of formula (II), a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof which process comprises coupling together a compound of formula (XII)



(XII)

where L is a leaving group.

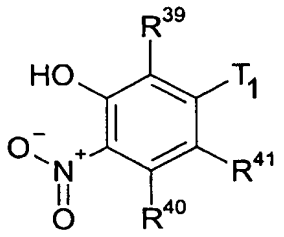
and an appropriate amine, where any functional group is optionally protected;

and thereafter, if necessary:

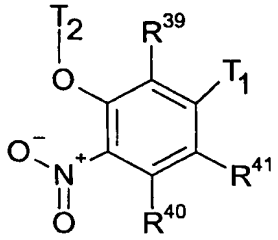
a) removing any protecting group; and

b) forming a pharmaceutically acceptable salt or in vivo hydrolysable derivative.

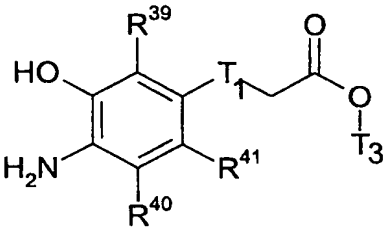
Alternative specific routes for preparing compounds of formula (I), where A is benzoxazolyl, B is phenyl and R^1 is hydrogen are as follows. In the compounds of formulae (XIII) to (XVI) and R^{39} to R^{41} are substituents on the bicyclic ring system A as hereinbefore defined



(XIII)



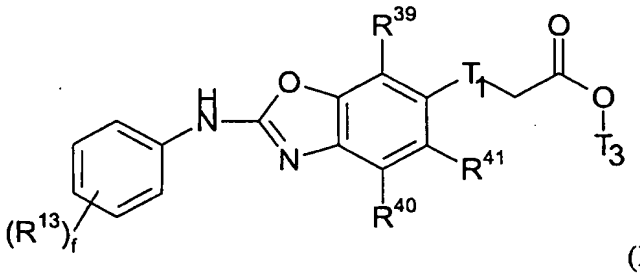
(XIV)



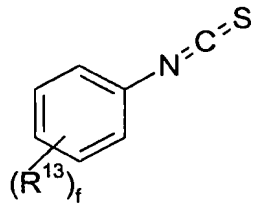
(XV)

o-Nitrophenols of the type (formula (XIII) $T_1 = CH_2.CO_2Me$) can be prepared by a variety of methods which include displacement of fluorine in compounds (formula (XIII) T_1 = F) by diethyl sodiomalonate followed by hydrolysis and decarboxylation; and Pd mediated coupling with diethyl malonate of the compound (formula (XIII) T_1= Br and where the hydroxy is preferably protected). Displacement of the fluorine in compounds of the type (formula (XIV); T_1 =F, T_2= Bn) with hydroxide ion gives phenols (formula (XIV) T_1 = OH T_2= Bn) which can be reacted under basic conditions with t-butylbromoacetate to give t-butyl phenoxyacetates ((formula (XIV) $T_1 = OCH_2CO.O^tBu$, T_2= Bn). The benzyl protecting group can be removed (e.g. Pd/H_2, Pd/ ammonium formate or BBr_3) to yield a nitro phenol ((formula (XIV) $T_1 = OCH_2CO.O^tBu$, T_2= H). O-nitrophenols of the type (formula (XIV) $T_1 = CH_2.CO_2Me$, T_2= Bn) can be prepared by Pd mediated coupling with diethyl malonate of the compound (formula (XIV) T_1= Br, T_2= Bn). The benzyl protecting group can be removed as described above.

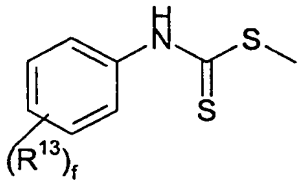
Nitro phenols prepared as above can be reduced to an amino compound (formula (XIV) T_1 = oxygen or direct bond, T_3= Me or ^{t}Bu) using, for example Pd/H_2, Pd/ ammonium formate or Fe/HOAc. The amino compounds (formula(XV)) are unstable and can be converted in situ into the corresponding alkyl 2-phenylaminobenzoxazole-6-acetate (formula (XVI) T_1 = O or direct bond, T_3= Me, ^{t}Bu) using an appropriately



(XVI)



(XVII)

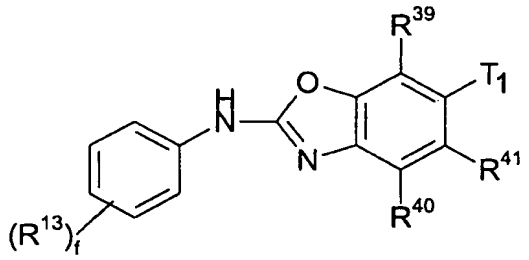


(XVIII)

substituted phenyl isothiocyanate (XVII) or with an appropriately substituted phenyl dithiocarbamate (XVIII) in the presence of mercuric oxide. Deprotection of these esters will yield the corresponding acids ((formula (XVI), T_3 = H).

An alternative route for the preparation of anilinobenzoxazoles and which avoids the need to use toxic mercuric oxide involves reacting o-hydroxyureas using Mitsunobu reaction conditions, i.e a trisubstituted triphosphine, for example tributylphosphine or triphenylphosphine and an azodicarbonyl compound, for example 1,1'-(azodicarbonyl)dipiperidine (ADDP) or diethylazodicarboxylate. This reaction can be carried out under mild conditions, is tolerant of a wide range of functional groups, is reliably reproducible and avoids the problem of handling and disposing of toxic reagents and residues. It also eliminates the potential for contaminating the final product with traces of mercury compounds.

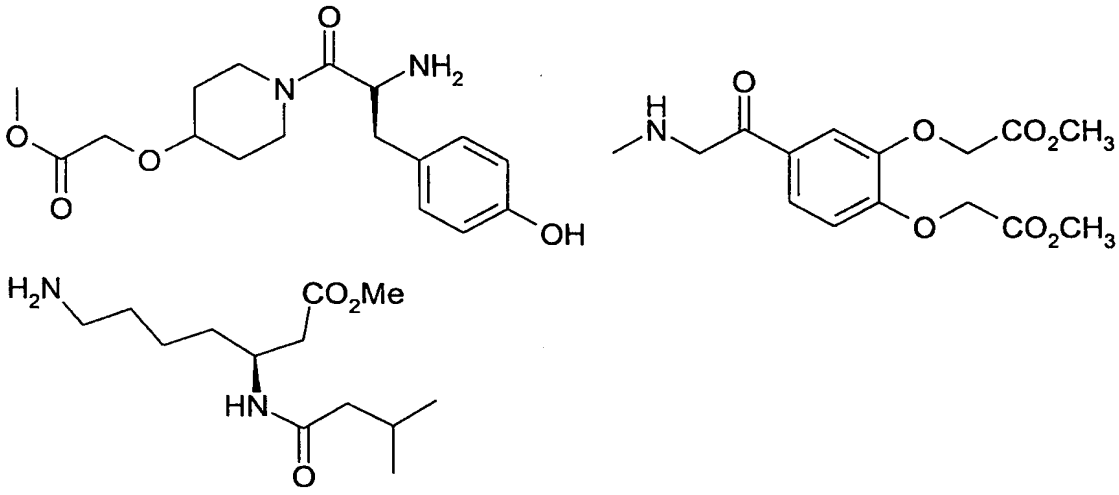
Starting from compounds of formula (XIII), T_1 = CO_2H and using similar methods, anilinobenzoxazoles acids of formula (XIX), T_1 = CO_2H may be prepared.



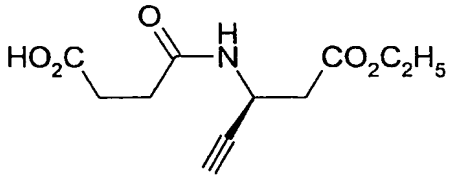
(XIX)

Compounds of formula (XIX), $T_1 = CO_2H$ may be converted into amines of formula (XIX), $T_1 = NH_2$ by known methods e.g. the Curtius Reaction.

The anilinobenzoxazoles acids prepared as above may be coupled with amines to form compounds of formula (I) according to the invention. Suitable amines are those based on $\alpha_{IIb}\beta_3$ antagonists such as those described in S A Mousa et al., (1997), Drug Discovery Today, 2 (5), 187-199, US 5256812 and EP 560730 and include:



The anilinobenzoxazoles amines prepared as above may be coupled with carboxylic acids to prepare compounds of formula (I) according to the invention. A suitable acid based on $\alpha_{IIb}\beta_3$ antagonists such as those described in S A Mousa et al., (1997), Drug Discovery Today, 2 (5), 187-199 includes:



Other suitable amines and acids can be derived from compounds which inhibit the interaction between the integrin $\alpha_{IIb}\beta_3$ and its ligand fibrinogen as hereinbefore defined.

The reactions to couple the above acids to the above amines are to couple a compound of formula (XII) to an appropriate amine are performed under standard coupling conditions for forming peptide bonds. They can be performed either on a solid support (Solid Phase Peptide Synthesis) or in solution using normal techniques used in the synthesis of organic compounds. With the exception of the solid support, all the other protecting groups, coupling agents, deblocking reagents and purification techniques are similar in both the solid phase and solution phase peptide synthesis techniques.

During the reaction, amino acid functional groups may, if necessary, be protected by protecting groups, for example BOC (tert-butoxycarbonyl). Such groups can be cleaved when necessary using standard techniques such as acid or base treatment.

Suitable protecting groups for the protection of the carboxyl groups include esters.

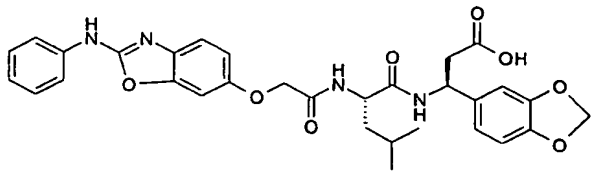
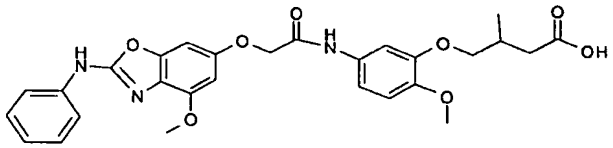
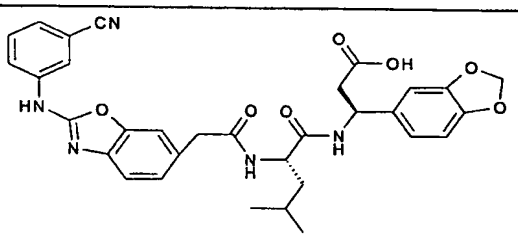
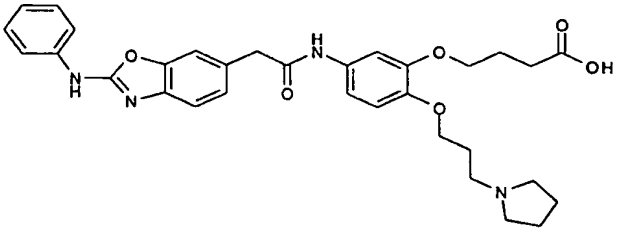
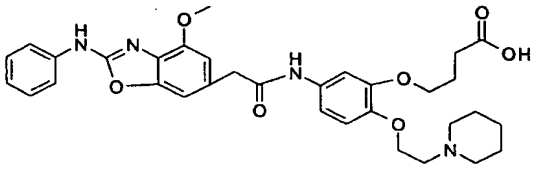
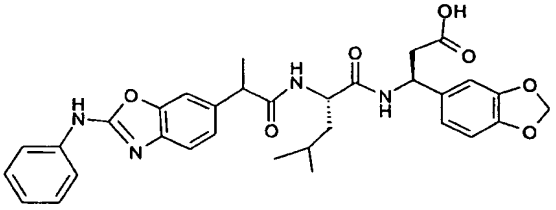
Coupling reagents for forming peptide bonds include the commonly used azide, symmetrical anhydride, mixed anhydride and various active esters and carbodiimides. In the case of carbodiimides, additives such as 1-hydroxybenzotriazole and N-hydroxysuccinimide may also be added. Other coupling reagents include 1H-benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP), (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)] and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).

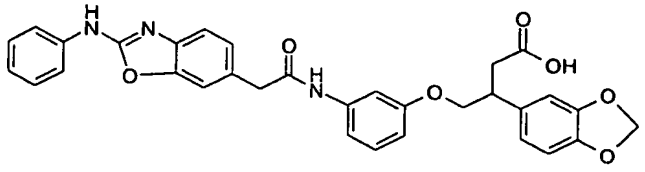
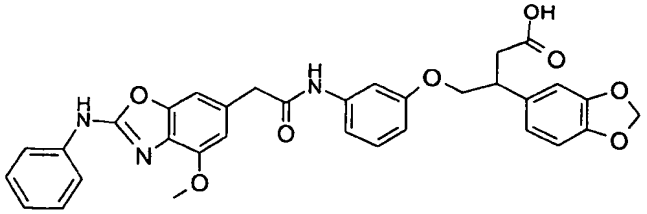
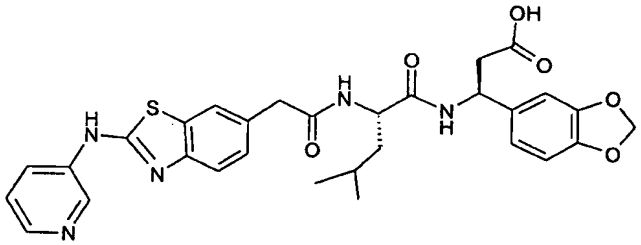
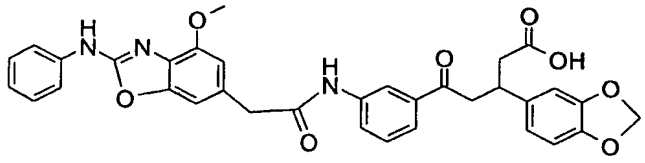
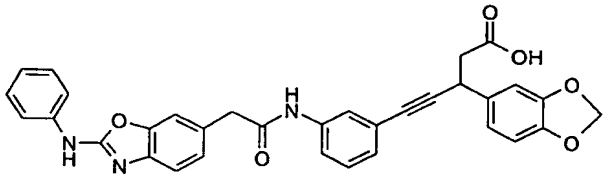
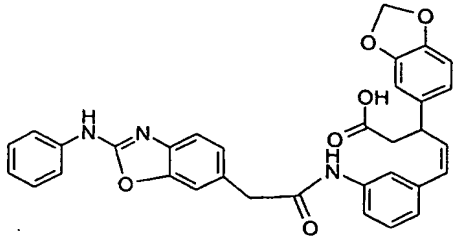
The coupling reactions can be performed at temperatures between -20°C to 40°C. The time of the reaction can vary such as between 10 minutes and 24 hours.

Suitable purification methods for the intermediates and final products include chromatographic techniques such as high pressure liquid chromatography (HPLC) along with many other standard techniques used in organic chemistry (e.g. solvent extraction and crystallisation).

It will be understood that all amino acids are the natural isomers unless otherwise stated.

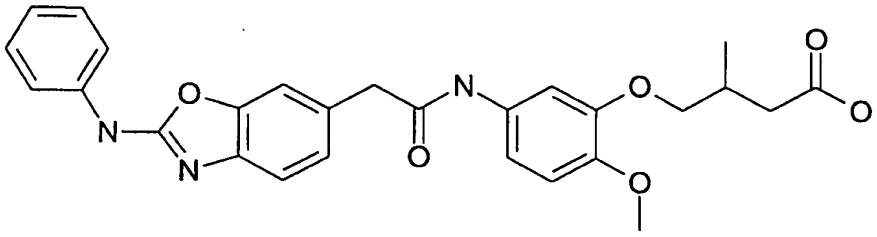
The invention is further limited by the following biological test methods, data and non-limiting examples, as described below and with reference to Table 1. For the avoidance of doubt, representative structures and names of a number of examples are given in Table 2 below.

Table 2		Structure
Ex. No.	**Name**	**Structure**
12	2-Anilino-6-[2-carboxy-1-(benzo[1,3]dioxyol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethoxy]benzoxazole	
24	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-methoxy-anilinocarbonylmethoxy}benzoxazole	
40	2-(3-Cyanophenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole	
78	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N-pyrrolidinylpropoxy)-anilinocarbonylmethyl}benzoxazole	
79	2-Anilino-4-methoxy-6-{3-[3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl}benzoxazole	
101	2-anilino 6-[1-(2-Carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonyl}ethyl] benzoxazole.	

106	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole	
114	2-Anilino-4-methoxy-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole	
125	2-(Pyrid-3-ylamino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly 5-yl)ethylaminocarbonyl(S)-(2 methylpropyl)methylaminocarbonylmethyl]benzothiazole	
135	2-Anilino-4-methoxy-6-{3-[1-oxo-3-(benzo[1,3]dioxyol 5-yl)-4-carboxybutyl]anilinocarbonyl methyl}benzoxazole	
136	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxybut-1-ynyl]anilinocarbonylmethyl}benzoxazole	
138	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxy-(Z)-but-1-enyl]anilinocarbonylmethyl}benzoxazole	

Examples

Example 1 - Preparation of 4-(5-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-2-methoxyphenoxy)-3-methylbutanoic acid



Methyl 4-(5-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-2-methoxyphenoxy)-3-methyl butanoate (0.07g) was treated in dimethylsulphoxide (1ml) with 2M sodium hydroxide (0.5ml) and stirred for 0.5 hr. The resulting mixture was then acidified with acetic acid and diluted with water. The precipitated product was filtered and washed with water to give the acid (0.05g)

1H nmr (DMSO d6): 1.0d (d) 3H; 2.1-2.5d, (m), 3H; 3.65d, (s), 2H; 3.7d, (s), 3H; 3.75d, (m), 2H; 6.85d, (d), 1H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.15d (d), 1H; 7.35d, (m) 6H; 7.7d, (d), 2H; 10.0d, (s) ,1H; and 10.58d, (bs), 1H.

Mass spectrum: M+H at 490.

a) Preparation of 2-(benzyloxy)-4-fluoro-nitrobenzene

To 2-nitro-5-fluorophenol (6.28g) in acetonitrile (50ml) was added potassium carbonate (5.6g) and benzyl bromide (7.2g). The mixture was stirred at reflux for 2hrs, added to water and extracted with diethyl ether. The organic layer was washed with brine, dried and evaporated to dryness to give 2-(benzyloxy)-4-fluoro-nitrobenzene (10.2g) as a solid.

nmr (deuterochloroform): 5.2d (s), 2H; 6.7d, (m), 1H; 6.8d (q), 1H; 7.4d (m), 5H; 8.0d, (q), 1H;

b) Preparation of dimethyl-(3-benzyloxy-4-nitrophenyl)malonate

To dimethylmalonate (6.6g) in N-methylpyrrolidone (30ml) was added, in portions, sodium hydride (60% dispersion, 2g) and the mixture stirred until all evolution of hydrogen had ceased. 2-(benzyloxy)-4-fluoro-nitrobenzene (7.51g) was then added and the mixture heated at 80°C for 4hrs., cooled, added to water, acidified with 2M hydrochloric acid and extracted with

ethyl acetate (2 times). The organic extracts were combined, washed with water, brine, dried and evaporated to dryness. The residue was triturated with diethyl ether and filtered to give dimethyl-(3-benzyloxy-4-nitrophenyl)malonate (6.6g).

nmr (deuterochloroform): 3.75d, (s), 6H; 4.6d, (s), 1H; 5.25d, (s), 2H; 7.05d, (q), 1H; 7.4d, (m), 6H; 7.8d, (d), 2H.

c) Preparation of 3-hydroxy-4-nitrophenylacetic acid

The malonic ester from step b) (3g) was heated at 100°C in a mixture of acetic acid (20ml) and conc. hydrochloric acid (10ml) for 2 hrs. and then evaporated to dryness. The residue was triturated with a mixture of diethyl ether and hexane to give 3-hydroxy-4-nitrophenylacetic acid as a yellow solid (1.4g) isolated by filtration.

nmr (DMSOd6): 3.6d, (s), 2H; 6.8d, (d), 1H; 7.0d, (s), 1H; 7.8d, (d), 1H; 10.5d, (bs), 1H; 12.8d, (bs), 1H.

d) Preparation of methyl 3-hydroxy-4-nitrophenylacetate

3-hydroxy-4-nitrophenylacetic acid (1.1g) was refluxed in methanol (20ml) containing 0.5ml of conc. sulphuric acid for 4hrs., diluted with water and extracted with diethyl ether. The organic layer was separated, washed with aqueous sodium bicarbonate, brine, dried and then evaporated to dryness to give methyl 3-hydroxy-4-nitrophenylacetate (1.2g) as a gum which crystallised on standing.

Nmr (deuterochloroform): 3.65d, (s), 2H; 3.7d, (s), 3H; 6.9d, (q), 1H; 7.1d, (d), 1H; 8.05d, (d), 1H; 10.6d, (s), 1H.

e) Preparation of methyl 2-phenylaminobenzoxazole-6-acetate

To methyl 3-hydroxy-4-nitrophenylacetate (0.58g) in ethanol (10ml) was added 0.1g of 10% palladium/carbon catalyst and the mixture stirred under an atmosphere of hydrogen for 1hr. and the catalyst then removed by filtration. To the filtrate was added phenylisothiocyanate (0.41g) and the mixture allowed to stand for 1 hr., and then yellow mercuric oxide (1g) added and the solution stirred at reflux for 3hrs., cooled, filtered and evaporated to dryness. The residue was purified by chromatography on silica using an increasingly polar mixture of ethyl acetate/hexane and the appropriate fraction yielded methyl 2-phenylaminobenzoxazole-6-acetate as a white solid (0.6g).

nmr (deuterochloroform): ~3.7d, (s), 2H; ~3.7d, (s), 3H (distinct singlets but very close); 7.1d, (m), 2H; 7.4d, (m), 4H; 7.3d, (s), 1H; 7.6d, (d), 2H.

f) Preparation of 2-phenylaminobenzoxazole-6-acetic acid

To methyl 2-phenylaminobenzoxazole-6-acetate (0.28g) in a mixture of dimethyl sulphoxide (1ml) and tetrahydrofuran (1ml) was added 2M sodium hydroxide (1ml). The mixture was stirred for 2 hrs. then acidified with acetic acid and diluted with water and the precipitate filtered and washed with water and dried to give 2-phenylaminobenzoxazole-6-acetic acid (0.24g) as a white solid.

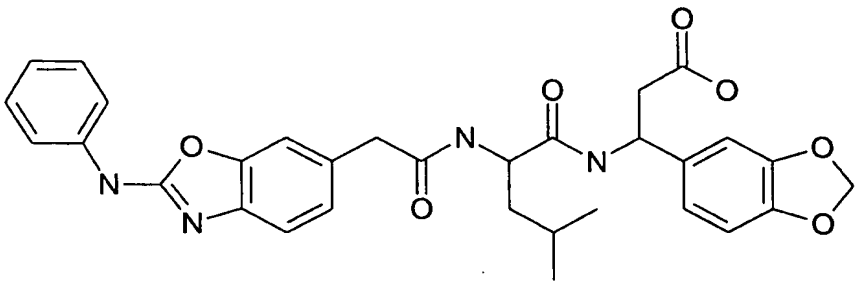
nmr (DMSOd6): 3.6d, (s), 2H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.3d (m), 4H; 7.75d, (d), 2H; 10.55d, (bs), 1H.

g) Preparation of Methyl 4-(5-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-2-methoxyphenoxy)-3-methyl butanoate

To a mixture of 2-phenylaminobenzoxazole-6-acetic acid(0.067g), methyl 3-methyl-4-(2-methoxy-5-aminophenoxy)butyrate(0.057g), hydroxybenzotriazole (0.067g), and N-methylmorpholine(0.05ml) in dimethylformamide(0.25ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(0.095g). The resultant mixture was stirred for 48hrs then added to water and extracted with ethyl acetate. The organic layer was separated, washed with aqueous acetic acid, brine, aqueous sodium bicarbonate (2 times), dried and evaporated to dryness. The residue was purified by purified by chromatography on silica using an increasingly polar mixture of ethyl acetate/dichloromethane and the appropriate fraction yielded, after evaporation to dryness, a solid which was triturated with a mixture of diethylether/hexane to give the product (0.08g) as a purple-pink solid.

^{1}H nmr (DMSOd6/Acetic d4): 1.0d, (d), 3H; 2.1-2.5d, (m), 3H; 3.5d (s), 3H; 3.65d, (s), 2H; 3.7d, (s), 3H; 3.75d, (m), 2H; 6.85d, (d), 1H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.15d (d), 1H; 7.35d, (m), 4H; 7.4d, (s), 1H; 7.7d, (d), 2H.

Example 2 - Preparation of 3-[(2-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid



Methyl 3-[(2-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl)propanoate (0.19g) was treated in dimethylsulphoxide (1ml) with 2M sodium hydroxide (0.5ml) and stirred for 0.5 hr. The resulting mixture was then acidified with acetic acid and diluted with water. The precipitated product was filtered and washed with water to give the acid (0.18g).

nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.35d, (m), 2H; 1.4d, (m), 1H; 2.6d, (m), 2H; 3.5d (q), 2H; 4.3d, (q), 1H; 5.05d, (q), 1H; 5.95d, (d), 2H; 6.7d, (m), 3H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.35d (m), 4H; 7.75d (d), 2H; 8.15d, (d), 1H; 8.4d, (d), 1H; 10.55d, (bs), 1H.

Mass spectrum M+H at 573.

a) Preparation of Methyl 3-(1,3-benzodioxol-5-yl)-3-({2-[tert-butoxycarbonyl)amino]4-methylpentanoyl}amino)propanoate

HOBT (255mg) was added to a solution of N -(t-butoxycarbonyl)leucine (297mg) in DMF (5ml), followed by 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (273mg) and the solution stirred for 15 min. Methyl 3-amino-3-(3,4-methylenedioxyphenyl) propionate(185mg) (prepared according to the method described in WO96/22966 (Biogen) at pages 52 to 55 and incorporated herein by reference) was dissolved in DMF (5ml) and triethylamine (140µl) and the resultant solution added to the solution of the N-(t-butoxycarbonyl)leucine activated ester followed by diisopropylethylamine (100µl). The mixture was stirred overnight at ambient temperature. The mixture was added to ethyl acetate(30ml), washed with water (2x5ml), 5% citric acid (5ml), water (5ml), saturated sodium bicarbonate solution (5ml), water (5ml), saturated brine (5ml), dried ($MgSO_4$) and evaporated to give methyl N-(t-butoxycarbonyl)3-(leucyl)amino-3-(3,4-methylenedioxyphenyl) propionate.

1H NMR (DMSO-d6, 300 MHz, ppm) : 0.9(6H, m), 1.3-1.5(3H,m), 2.7(2H,m), 3.5(3H,s), 4.8-4.9(1H,m), 5.1-5.2(1H, m), 5.9(2H,s), 6.7-6.9(4H,m), 8.2(1h,d), : m/Z 437 (M+H) .

b) Preparation of Methyl 3-[(2-amino-4-methylpentanoyl)amino]-3-(1,3 benzodioxol-5-yl)propanoate

Methyl 3-(1,3-benzodioxol-5-yl)-3-({2-[tert-butoxycarbonyl)amino]4-methylpentanoyl}amino)propanoate (10g) was treated with 90% TFA in water(100ml). The mixture was stirred for 30 min and the TFA and water were then removed by evaporation.

The residue was purified by preparative HPLC on a C18 silica column eluting with acetonitrile/water/0.1% TFA to give a gummy solid on evaporation of appropriate fractions. This was dissolved in ethyl acetate (50ml) and washed twice with saturated sodium bicarbonate solution(10ml), once with saturated brine(10ml), dried ($MgSO_4$) and evaporated to give methyl 3-(S-leucylamino)-3-[–benzo[1,3]dioxol-5-yl)phenyl]propanoate 1H NMR (DMSO-d6, 300 MHz, ppm) : 0.8(6H, m), 1.3-1.5(2H,m), 1.5-1.6(1H,m), 2.7(2H,m), 3.3-3.4(1H,m), 3.5(3H,s), 4.9-5.3(2H,b), 5.1-5.2(1H, m), 6.0(2H,s), 6.7-6.9(3H,m), 8.4-8.5(1H,d), : m/Z 337 (M+H).

c) Preparation of Methyl 3-[(2-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl)propanoate

To a mixture of 2-phenylaminobenzoxazole-6-acetic acid (0.134g) (made as described in example 1), methyl 3-[(2-amino-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl)propanoate (0.202g), hydroxybenzotriazole (0.135g), N-methylmorpholine (0.2ml) in dimethylformamide (1ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.191g). The mixture was stirred for 48hrs then added to water and extracted with ethyl acetate. The organic layer was separated, washed with aqueous acetic acid, brine, aqueous sodium bicarbonate (2 times), dried and evaporated to dryness. The residue was triturated with dichloromethane to give the product as a white solid (0.195g).

nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.35d, (m), 2H; 1.4d, (m), 1H; 2.6d, (m), 2H; 3.35d, (s), 3H; 3.5d (s), 2H; 4.3d, (q), 1H; 5.05d, (q), 1H;
5.95d, (d), 2H; 6.7d, (m), 3H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.35d (m), 4H;
7.75d (d), 2H; 8.15d, (d), 1H; 8.4d, (d), 1H.

Mass spectrum M+H at 588.

Example 3 - Preparation of 4-[5-({2-[2-(3-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino]-2-methoxyphenoxy}-3-methylbutanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 1
1H nmr (DMSO d6): 1.0d (d) 3H; 2.1-2.6d, (m), 3H; 3.6-3.8d, (m), 7H; 6..75-6.9d(m)2H; 7.05d, (d), 1H; 7.1d, (d), 1H; 7.3-7.5d, (m) 5H; 7.75d, (d), 1H; 10.0d, (s) ,1H; and 10.85d, (bs), 1H.

m/e508 $(MH)^+$.

a) Preparation of Methyl 4-[5-({2-[2-(3-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino]-2-methoxyphenoxy}-3-methylbutanoate

This was prepared {through the intermediates methyl-2-(3-fluorophenylamino) benzoxazole-6-acetate[m/e301, $(MH)^+$]and 2-(3-fluorophenylamino)benzoxazole-6-acetic acid[m/e287, $(MH)^+$] }by the series of processes described in Example 1e) to 1g) using 3- fluorophenyl isothiocyanate in place of phenyl isothiocyanate in step e)

1H nmr (DMSO d6): 1.0d (d) 3H; 2.2-2.6d, (m), 3H; 3.6d, (s), 3H; 3.65-3.8d, (m), 7H; 6.75-6.9d(m)2H; 7.05d, (d), 1H; 7.1d, (d), 1H;

7.3-7.5d, (m) 5H; 7.75d, (d), 1H; 10.0d, (s) ,1H; and 10.84d, (bs), 1H.

m/e522 $(MH)^+$.

Example 4 - Preparation of 4-[2-Methoxy-5-({2-[2-(2-toluidino)-1,3-benzoxazol-6-yl]acetyl}amino)-phenoxy]butanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 1. 1H nmr (DMSO d6): 1.0d (d) 3H; 2.1-2.6d, (m), 6H; 3.6-3.8d,(m), 7H; 6.85d(m)1H; 7.0-7.3d, (m) 7H; 7.4d,(s),1H; 7.8 d, (d),1H; 9.6d, (bs), 1H; 10.0d,(s) ,1H.

m/e504 $(MH)^+$.

a) Preparation of Methyl 4-[2-methoxy-5-({2-[2-(2-toluidino)-1,3-benzoxazol-6-yl]acetyl}amino)-phenoxy]butanoate

This was prepared {through the intermediates methyl-2-(2-methylphenylamino) benzoxazole-6-acetate[m/e297, $(MH)^+$]and 2-(2-methylphenylamino)benzoxazole-6-acetic acid[m/e283, $(MH)^+$]} by the series of processes described in Example 1e) to 1g) using 2-methylphenyl isothiocyanate in place of phenyl isothiocyanate in step e)

1H nmr (DMSO d6):1.0d (d) 3H; 2.2-2.6d, (m), 6H; 3.65-3.8d, (m), 10H;6.85d(d)1H; 7.0-7.3d, (m), 7H; 7.4d,(s),1H; 7.8d, (d), 1H; 9.6d, (s), 1H; 10.0d, (s) ,1H.

m/e518 $(MH)^+$.

Example 5 - Preparation of 3-(1,3-benzodioxol-5-yl)-3-{[2-({2-[2-(3-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 2.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H;

2.6d, (m), 2H; 3.5d (q), 2H; 4.3d, (m), 1H; 5.05d, (m), 1H; 5.95d, (s), 2H; 6.7-6.9d, (m), 4H; 7.1d, (d), 1H; 7.4d (m), 4H; 7.75d (d), 1H; 8.15d, (d), 1H;

8.4d, (d), 1H; 10.8d, (bs), 1H; 12.2d, (bs), 1H.

m/e591 $(MH)^+$.

a) Preparation of Methyl 3-(1,3-benzodioxol-5-yl)-3-{[2-({2-[2-(3-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino)-4-methylpentanoyl]amino}propanoate

This was prepared by the process described in Example 2c) using 2-(3-fluorophenylamino)benzoxazole-6-acetic acid in place of 2-phenylaminobenzoxazole-6-acetic acid.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H; 2.7d, (m), 2H; 3.5d (s),3 H; 3.55d (s), 2H; 4.3d, (m), 1H; 5.1d, (m), 1H; 5.95d, (s), 2H; 6.7-6.9d, (m), 4H; 7.1d, (d), 1H; 7.4d (m), 4H; 7.75d (d), 1H; 8.2d, (d), 1H; 8.4d, (d), 1H; 10.8d, (bs), 1H.

m/e605 $(MH)^+$.

Example 6 - Preparation of 3-(1,3-benzodioxol-5-yl)-3-{[4-methyl-2-({2-[2-toluidino)-1,3-benzoxazol-6-yl]acetyl}amino)pentanoyl]amino}propanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 2.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H; 2.25d, (s), 3H; 2.6d, (m), 2H; 3.5d (q), 2H; 4.3d, (m), 1H; 5.05d, (m), 1H; 5.95d, (m), 2H; 6.7d(d) 1H; 6.8d, (m), 2H; 7.05d, (m), 2H; 7.2d (m), 3H; 7.3d (s), 1H; 7.8d (d), 1H; 8.1d, (d), 1H; 8.35d, (d), 1H; 9.6d, (bs).

m/e587 $(MH)^+$.

a) Preparation of Methyl 3-(1,3-benzodioxol-5-yl)-3-{[4-methyl-2-({2-[2-toluidino)-1,3-benzoxazol-6-yl]acetyl}amino)pentanoyl]amino}propanoate

This was prepared by the process described in Example 2c) using 2-(2-methylphenylamino)benzoxazole-6-acetic acid in place of 2-phenylaminobenzoxazole-6-acetic acid.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H; 2.25d, (s), 3H; 2.7d, (m), 2H; 3.5d (m), 5H; 4.3d, (m), 1H; 5.1d, (m), 1H; 5.95d, (m), 2H; 6.7d(d) 1H; 6.8d, (d), 1H; 6.85d, (s), 1H; 7.05d, (m), 2H; 7.2d (m), 3H; 7.3d (s), 1H; 7.8d (d), 1H; 8.1d, (d), 1H; 8.4d, (d), 1H; 9.6d, (s).

m/e601 $(MH)^+$.

Example 7 - Preparation of 4-(3-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino} phenoxy)butanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 1.

1H nmr (DMSO d6): 1.9d, (m), 2H; 2.3d, (t), 2H; 3.7d, (s), 2H; 3.9d, (m), 2H; 6.8d, (d), 1H; 7.0d, (t), 1H; 7.1d, (m), 3H; 7.3d (m), 4H; 7.45d, (s) 1H; 7.75d, (d), 2H; 10.1d, (bs) ,1H; and 10.55d, (bs), 1H.

m/e444 $(MH)^-$.

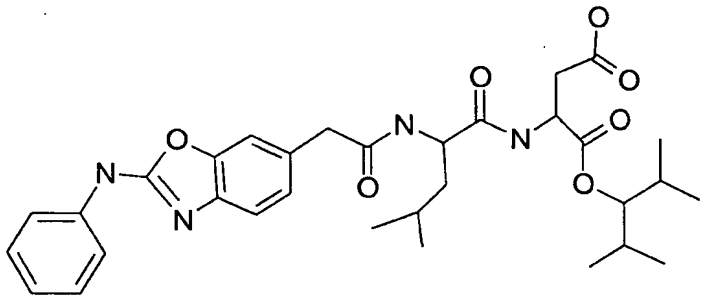
a) Preparation of Methyl 4-(3-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino} phenoxy)butanoate

This was prepared by the process described in Example 1g) but using methyl-3-aminophenoxybutyrate as the amino component in the coupling reaction.

1H nmr (DMSO d6): 1.9d, (m), 2H; 2.4d, (t), 2H; 3.6d, (s), 3H ; 3.7d, (s), 2H; 3.95d, (t), 2H; 6.6d, (d), 1H; 7.0d, (t), 1H; 7.05-7,2d, (m), 3H; 7.3d (m), 4H; 7.45d, (s) 1H; 7.75d, (d), 2H; 10.1d, (bs) ,1H; and 10.55d, (bs), 1H.

m/e460 $(MH)^+$

Example 8 - Preparation of 3-[(2-{[2-(2-anilino-1,3-benzoxazol-6-yl)acetyl]amino}-4-methylpentanoyl)amino]-4-(1-isopropyl-2-methylpropoxy)-4-oxobutanoic acid.



A mixture of 2-(2-phenylamino-benzoxazol-6-yl)-acetylamino-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester(120mg), ethanol(10mL) and 10% Pd on Carbon catalyst(50mg) was stirred under hydrogen at room temperature and atmospheric pressure for18 hours. The mixture was filtered, the filtrate evaporated to dryness and the residue triturated with an ethyl acetate /diethyl ether mixture to give the product (72mg) as an off white solid.

1H nmr (DMSO d6): 0.85-0.95d, (m), 18H; 1.45d, (m), 2H; 1.55d, (m),1H; 1.8d, (m), 2H; 2.5- 2.75d, (m), 2H; 3.5d, (q), 2H; 4.35d, (m), 1H; 4.45d, (m), 1H; 4.65d,(m), 1H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.3-7.4d (m), 4H;7.75d, (d) 2H; 8.2d, (d), 1H; 8.45d, (d), 1H; 10.7d, (bs) ,1H. m/e593 $(MH)^-$.

a) Preparation of BOC-aspartic acid-α-(2,5-dimethylpentyl)-β-benzyl diester

A mixture of BOC-aspartic acid-β-benzyl ester(3.23g), dichloromethane(20mL), 2,4-dimethylpentanol(1.51g) and dicyclohexylcarbodiimide(2.06g) was stirred and treated with 4-dimethylaminopyridine(20mg).The mixture was stirred for 1 hour, filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography on silica using an increasingly polar mixture of dichloromethane and ethyl acetate and the appropriate fractions combined and evaporated to dryness to give BOC-aspartic acid-α-(2,5-dimethylpentyl) -β-benzyl diester as a gum(3.55g). [m/e422 $(MH)^+$]

b) Preparation of aspartic acid-α-(2,5-dimethylpentyl)-β-benzyl diester

A solution of BOC-aspartic acid-α-(2,5-dimethylpentyl)-β-benzyl diester(3.4g) in dichloromethane(10mL) was treated with trifluoroacetic acid(10mL) and the mixture was stirred at room temperature for 2 hours then evaporated to dryness. The residue was stirred with a mixture of water(10mL) and ethyl acetate(30mL) and basified with potassium hydrogen carbonate. The organic phase was separated, washed with brine, dried and evaporated to dryness to give aspartic acid-α-(2,5-dimethylpentyl)-β-benzyl diester as a gum(2.7g). [m/e322 $(MH)^+$]

c) Preparation of BOC-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester

A mixture of aspartic acid-α-(2,5-dimethylpentyl)-β-benzyl diester (1.6g), BOC-leucine(1.45g), hydroxybenzotriazole (1g), N-methylmorpholine(0.7ml), dimethylformamide(10ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(1.35g) was stirred for 48hrs. The mixture was partitioned between water and ethyl acetate, the organic layer was separated and washed successively with 1M hydrochloric acid, brine, 1M sodium hydroxide (2 times) and brine and then dried and evaporated to dryness. The residue was triturated with ether/hexane to give BOC-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester as a white solid (1.55g). [m/e535 $(MH)^+$]

d) **Preparation of leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester**

BOC-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester was deprotected with trifluoroacetic acid by the process described in b) to give leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester as a gum [m/4535 $(MH)^+$]

e) **Preparation of 2-(2-phenylamino-benzoxazol-6-yl)-acetylamino-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester**

A mixture of leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester(109mg), 2-(2-phenylaminobenzoxazole)-6-acetic acid(67mg), hydroxybenzotriazole (54mg), N-methylmorpholine(0.05ml), dimethylformamide(0.5ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(76mg) was stirred for 48hrs.The mixture was acidified with aqueous acetic acid and extracted with ethyl acetate. The organic layer was separated, washed successively with water, aqueous sodium hydrogen carbonate (2 times) and brine and then dried and evaporated to dryness. The residue was triturated with ether to give 2-(2-phenylamino-benzoxazol-6-yl)-acetylamino-leucyl-aspartic acid - α-(2,5-dimethylpentyl)-β-benzyl diester as a white solid (140mg).

1H nmr (DMSO d6): 0.85-0.95d, (m), 18H; 1.45d, (m), 2H; 1.55d, (m),1H; 1.8d, (m), 2H; 2.7d, (dd), 1H; 2.9d, (dd), 1H; 3.5d, (q), 2H; 4.35d, (m), 1H; 4.45d, (m), 1H; 4.7d,(m), 1H; 5.05d, (s), 2H; 7.0d, (t), 1H; 7.1d, (d), 1H; 7.2-7.4d (m), 9H;7.75d, (d) 2H; 8.2d, (d), 1H; 8.5d, (d), 1H; 10.53d, (bs) ,1H.

[m/e685 $(MH)^+$]

Example 9 - Preparation of 3-(1,3-benzodioxol-5-yl)-3-{[2-({2-[2-(4-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino)-4-methylpentanoyl]amino}propanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 2.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H;2.6d, (m), 2H; 3.5d (q), 2H; 4.3d, (m), 1H; 5.05d, (m), 1H; 5.95d, (s), 2H; 6.7-6.9d, (m), 4H; 7.1d, (m), 1H; 7.2d, (m), 2H; 7.35d (m), 2H; 7.75d (m), 2H; 8.15d, (m), 1H;

8.35d, (m), 1H; 10.55d, (bs), 1H.

m/e589 $(MH)^-$.

a) Preparation of methyl 3-(1,3-benzodioxol-5-yl)-3-[(2-{[2-(3-hydroxy-4-nitrophenyl)acetyl]amino}-4-methylpentanoyl)amino]propanoate

A mixture of 2-(3-hydroxy-4-nitro)phenylacetic acid(200mg), methyl 3-[(2-amino-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl)propanoate(336mg), hydroxybenzotriazole (270mg), N-methylmorpholine(0.2ml), dimethylformamide(2ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(300mg) was stirred for 48hrs.The mixture was partitioned between ethyl acetate and water and the organic layer was separated, washed successively with 1M hydrochloric acid, brine, aqueous sodium hydrogen carbonate and brine and then dried and evaporated to dryness. The residue was triturated with ether to give Methyl 3-S-3-(Benzo[1,3]dioxol-5-yl)-3-[2-(3-hydroxy-4-nitro)phenylacetyl-S-Leucylamino]-propanoate(320mg) as an off white solid.[m/e516,(MH)+]

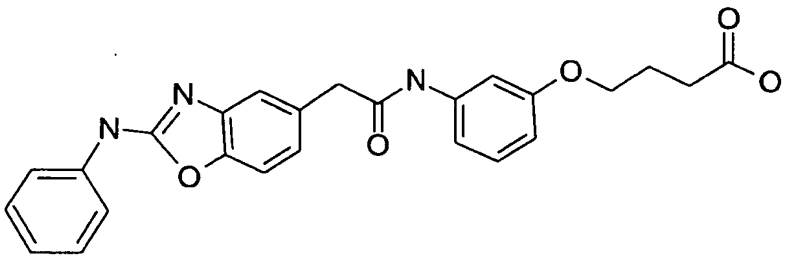
b) Preparation of Methyl 3-(1,3-benzodioxol-5-yl)-3-{[2-({2-[2-(4-fluoroanilino)-1,3-benzoxazol-6-yl]acetyl}amino)-4-methylpentanoyl]amino}propanoate

A mixture of methyl 3-(1,3-benzodioxol-5-yl)-3-[(2-{[2-(3-hydroxy-4-nitrophenyl)acetyl]amino}-4-methylpentanoyl)amino]propanoate(155mg), ethanol(2.5mL), tetrahydrofuran(2.5mL) and 10% palladium on carbon catalyst was stirred under hydrogen at room temperature and atmospheric pressure for 1.5 hour. 4-Fluorophenylisothiocyanate(46mg) was added and the mixture kept at room temperature for 2 hours .The mixture was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(115mg) and the mixture was stirred at room temperature for 48 hours and evaporated to dryness. The residue was partitioned between ethyl acetate and water and the organic phase was dried and evaporated to dryness. The residue was purified by flash chromatography on silica using an increasingly polar mixture of dichloromethane and ethyl acetate and the appropriate fractions combined and evaporated to dryness to give product (53 mg) as an off white solid.

1H-nmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H;2.7d, (m), 2H; 3.5d (m), 5H; 4.3d, (m), 1H; 5.1 d, (m), 1H; 5.95d, (s), 2H; 6.7-6.9d, (m), 4H; 7.1d, (m), 1H; 7.2d, (m), 2H; 7.35d (m), 2H; 7.75d (m), 2H; 8.15d, (d), 1H;
8.4d, (d), 1H; 10.58d, (bs), 1H.

m/e605 (MH)+

Example 10 - Preparation of 4-(3-{[2-(2-anilino-1,3-benzoxazol-5-yl)acetyl]amino} phenoxy)butanoic acid



This was prepared by hydrolysis of the methyl ester using the process described in Example 1.

1H nmr (DMSO d6): 1.9d, (m), 2H; 2.3d, (t), 2H; 3.7d, (s), 2H; 3.9d, (m), 2H; 6.6d, (d), 1H; 7.0-7.25d, (m), 4H; 7.3-7.5d (m), 5H; 7.7d, (d), 2H; 10.1d, (bs) ,1H; and 10.55d, (bs), 1H.

m/e444 $(MH)^-$.

a) Preparation of methyl 4-(3-{[2-(2-anilino-1,3-benzoxazol-5-yl)acetyl]amino} phenoxy)butanoate

The series of processes described in Example 1d) to 1f) was repeated using 4-hydroxy-3-nitrophenylacetic acid in place of 3-hydroxy-4-nitrophenylacetic acid to give the following intermediates:Methyl 4-hydroxy-3-nitrophenylacetate; m/e210$(MH)^-$.

Methyl 2-phenylaminobenzoxazole-5-acetate; m/e283 $(MH)^+$

2-Phenylaminobenzoxazole-5-acetic acid; m/e267 $(MH)^-$.

The process described in Example1g) was repeated using 2-Phenylaminobenzoxazole-5-acetic acid as the acid and methyl-3-aminophenoxybutyrate as the amino component in the coupling reaction to give methyl 4-(3-{[2-(2-anilino-1,3-benzoxazol-5-yl)acetyl]amino} phenoxy)butanoate as a white solid:

1H nmr (DMSO d6): 1.9d, (m), 2H; 2.45d, (t), 2H; 3.6d, (s), 3H ; 3.7d, (s), 2H; 3.95d, (t), 2H; 6.6d, (d), 1H; 6.9-7.2d, (m), 4H; 7.25-7,45d, (m), 5H; 7.75d, (d), 2H; 10.1d, (s) ,1H; and 10.65d, (s), 1H.

m/e460 $(MH)^+$

Example 11 - Preparation of 3-[(2-{[2-(2-anilino-1,3-benzoxazol-5-yl)acetyl]amino}-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl) propanoic acid

This was prepared by hydrolysis of the methyl ester using the process described in Example 2.

1Hnmr (DMSOd6): 0.7d, (d), 3H; 0.8d, (d), 3H; 1.3-1.5d, (m), 3H; 2.6d, (m), 2H; 3.5d (q), 2H; 4.25d, (q), 1H; 5.05d, (q), 1H; 5.95d, (s), 2H; 6.65-6.85d, (m), 3H; 7.0d, (m), 2H;

7.35d (m), 4H; 7.7d (d), 2H; 8.1d, (d), 1H;8.35d, (d), 1H; 10.1d, (s) ,1H; and 10.65d, (s), 1H.

m/e571 $(MH)^-$.

a) Preparation of Methyl 3-[(2-{[2-(2-anilino-1,3-benzoxazol-5-yl)acetyl]amino}-4-methylpentanoyl)amino]-3-(1,3-benzodioxol-5-yl) propanoate

This was made by the process described in example 2c) using 2-Phenylaminobenzoxazole-5-acetic acid in place of 2-Phenylaminobenzoxazole-6-acetic acid as the acid component in the Coupling. [m/e460 $(MH)^+$]

Examples 12 to 128 are described by reference to Table 1. This table describes the route for making the examples by reference to methods for

i) the final stage, i.e. removal of the acid protecting group

ii) the penultimate stage i.e. forming final product but with acid protecting group;

iii) preparing the benzoheterocyclic acid or the precursor to the benzoheterocycle; and

iv) preparing the appropriate amine for coupling to the benzoheterocyclic acid or

preparing an o-hydroxyurea with the amide bonds intact for processes in which the benzoheterocycle, typically a benzoxazole, is formed in the penultimate stage, i.e. formation of the benzoheterocycle mediated by mercuric oxide or the Mitsunobu reaction conditions,

all of which are described below.

The methods are described by reference to the final product or intermediate product of a particular example. It will be appreciated by the skilled person that the same reaction conditions can be used for analogous final products or intermediate compounds.

For example 46 to 60, 129 and 130 no nmr data is included since these examples were made by multiple parallel synthesis.

Table 1

Ex. No.	M-H	M+H	MS Comm--ent	1H NMR in DMSOd6	Final Stage	Penulti-mate Stage	Method for Benzo-heterocyc--lic Acid	Methods for amine to couple to Benzo-heterocyc--lic acid	Name
1		490		1.0(d),3H;2.1-2.5,(m),3H;3.65(s),2H;3.7(s),3H;3.75(m),2H;6.85,(d),1H;7.0(t),1H;7.1,(d),1H7.15(d),1H;7.35,(m),5H;7.7(d),2H;10.0,(s),1H;10.58(bs),1H.	Ia	A(i)	12a	4b, 5a, 6a	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-methoxy-anilinocarbonylmethyl} benzoxazole
2		573		0.7,(d),3H;0.8,(d),3H;1.35,(m),2H;1.4,(m),1H;2.6,(m),2H;3.5(q),2H;4.3,(q),1H;5.05,(q),1H;5.95,(d),2H;6.7,(m),3H;7.0,(t),1H;7.1,(d),1H;7.35d(m),4H;7.75d(d),2H;8.15,(d),1H;8.4,(d),1H;10.55,(s),1H.	Ia	A(i)	12a	29	2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
3		508		1.0(d),3H;2.1-2.6,(m),3H;3.65(s),2H;3.7(s),3H;3.75(m),2H;6.75-6.9(m),2H;7.0-7.5(m),7H;7.75(d),1H;9.9,1H;10.84(s),1H.	Ia	A(i)	12a	4b, 5a, 6a	2-(3-Fluoro-anilino)-6-{3-[2-methyl-3-carboxypropoxy-]-4-methoxy-anilinocarbonylmethyl} benzoxazole
4		504		1.0(d),3H;2.1(q),1H;2.2-2.3(m),5H;3.65(s),2H;3.7(s),3H;3.75(m),2H;6.85(d),1H;7.0-7.4(m),9H;7.8(d),1H;9.9,1H.	Ia	A(i)	12a	4b, 5a, 6a	2-(2-methyl-anilino)-6-{3-[2-methyl-3-carboxypropoxy-]-4-methoxy-anilinocarbonylmethyl} benzoxazole
5		591		0.7,(d),3H;0.8,(d),3H;1.3-1.5,(m),3H;2.6,(m),2H;3.5(q),2H;4.3,(m),1H;5.05,(m),1H;5.95,(s),2H;6.7-6.9,(m),4H;7.1,(d),1H;7.4(m),4H;7.75(d),1H;8.15,(d),1H;8.4,(d),1H;10.8,(bs),1H;12.2,(s),1H.	Ia	A(i)	12a	29	2-(3-Fluoroanilino) -6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

6		587		0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.3(s),3H;2.5-2.7(m),2H;3.5(m),2H;4.3(m),1H;5.05(m),1H;5.95(s),2H;6.7-6.8(m),3H;7.05(m),2H;7.2(m),3H;7.3(s),1H;7.8(d),1H;8.1(d),1H;8.35(d),1H;9.55(s),1H.	Ia	A(i)	12a	29	2-(2-methylanilino) 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
7	444			1.85(m),2H;2.35(t),2H;3.5(s),2H;3.9,(t),2H;6.6(d)1H;7.0,(t)1H;7.05-7.2,(m),3H;7.25-7.45,(m),5H;7.75,(d),2H;10.1(s),1H10.55,(s)1H.	Ia	A(i)	12a	4b, 5a	2-Anilino-6-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
8		593		0.85-0.95,(m),18H;1.45,(m),2H;1.55,(m),1H;1.8,(m),2H;2.5-2.75,(m),2H;3.5,(q),2H;4.35,(m),1H;4.45,(m),1H;4.65,(m),1H;7.0,(t),1H;7.1,(d),1H;7.3-7.4d(m),4H;7.75,(d)2H;8.2,(d),1H;8.45,(d),1H;10.7,(s),1H	II	A(i)	12a	29	2-anilino 6-[2-Carboxy-1-([2,4-dimethylpent-3-yl]oxycarbonyl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
9	589			0.7,(d),3H;0.8,(d),3H;1.3-1.5,(m),3H;2.6,(m),2H;3.5(q),2H;4.3,(m),1H;5.05,(m),1H;5.95,(s),2H;6.7-6.9,(m),4H;7.1,(m),1H;7.2,(m),2H;7.35(m),2H;7.75(m),2H;8.15,(m),1H;8.35,(m),1H;10.55,(bs)	Ia	A(i)	12a	29	2-(4-fluoroanilino) 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
10	444			1.9, (m), 2H; 2.3, (t), 2H; 3.7, (s), 2H; 3.9, (m), 2H; 6.6, (d), 1H; 7.0-7.25, (m), 4H; 7.3-7.5 (m), 5H; 7.7, (d), 2H; 10.1, (bs) ,1H; and 10.55, (bs), 1H. m/e444 (MH)-.	Ia	A(i)	12a	4b, 5a	2-Anilino-5-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
11	571			0.7,(d),3H;0.8,(d),3H;1.3-1.5,(m),3H;2.6,(m),2H;3.5d(q),2H;4.25,(q),1H;5.05,(q),1H;5.95,(s),2H;6.65-6.85,(m),3H;7.0,(m),2H;7.35d(m),4H;7.7d(d),2H;8.1,(d),1H;8.35,(d),1H;10.1,(s),1H;10.65,(s),1H	Ia	A(i)	12a	29	2-anilino 5-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

12	587			0.9(6H,dd), 1.3-1.6(3H,m), 2.5-2.7(2H,m), 4.4(1H,m), 4.5(2H,s), 5.0(1H,m), 5.9(2H,s), 6.7-6.9(4H,m), 7.0(1H,t), 7.2(1H,s), 7.3-7.4(3H,m), 7.7(2H,d), 8.0(1H,d), 8.6(1H,d), 10.5(1H,b)	1b	A(ii)	20	29	2-Anilino-6-[2-carboxy-1-(benzo[1,3]dioxyol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethoxy]benzoxazole
13		601		0.8-0.9(m),6H;1.3-1.45(m),1H;1.45-1.6(m),1H;1.6-1.75(m),1H;2.3(s),3H;2.65-2.8(m),2H;2.9(s),3H;3.8(m),2H;5.15(m),2H;5.95(s),2H;6.8(s),2H;6.85(s),1H;7.1(m).2H;7.2-7.3(m),5H;7.75(d),2H.	Ia	A(i)	12a	29	2-(2-methylanilino) 6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methyl(N-methyl)aminocarbonylmethyl]benzoxazole
14	570			0.7,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.6,(m),2H;3.5d(q),2H;4.3,(q),1H;5.05,(q),1H;5.95,(d),2H;6.65-6.9,(m),4H;7.15-7.3,(m),4H;7.7,(d),2H;8.0,(d),1H;8.35,(d),1H;9.3,(bs),1H.	Ia	A(i)	21	29	2-anilino 6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzimidazole
15		591		0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.5-2.7(m),2H;3.5-3.6(m),2H;4.25(m),1H;5.05(m),1H;5.95(s),2H;6.7-6.9(m),3H;7.1-7.4(m).6H;8.1(d),1H;8.2(t),1H;8.35(d),1H.	Ia	A(i)	12a	29	2-(2-fluoroanilino) 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
16		641		0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.5-2.7(m),2H;3.5-3.6(m),2H;4.25(m),1H;5.05(m),1H;5.95(s),2H;6.7-6.9(m),3H;7.1(d),1H;7.2(s).1H;7.45(d),2H;7.8(s),2H;8.15(d),1H;8.35(d)1H.	Ia	A(i)	12a	29	2-(3,5-dichloroanilino) 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
17		619		0.8(t),6H;1.4(m),3H;2.65(m),2H;3.9(s),3H;4.4(m),1H;4.55(s),2H;5.05(m),1H;5.95(s),2H;6.55(d),1H;6.7-6.9(m),4H;7.0(t),1H;7.3(t),2H;7.7(d),2H;7.95(d),1H;8.5(d),1H;10.4(s),1H;12.2(s),1H.	Ia	A(i)	20	29	2-anilino-4-methoxy 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethoxy]benzoxazole

18	584	586		0.7,(d),3H;0.8,(d),3H;1.35,(m),2H;1.4,(m),1H;2.6,(m),2H;3.5d(q),2H;3.65,(s),3H 4.3,(q),1H;5.05,(q),1H;5.95,(d),2H;6.65-6.85,(m),3H;6.9-7.0,(m),2H;7.2-7.35,(m),4H;7.8(d),2H;8.1,(d),1H;8.5,(d),1H;8.9,(s)1H	Ia	A(i)	22	29	1-methyl-2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzimidazole
19	465			0.9(6H,dd), 1.0(3H,t), 1.4(2H,m), 1.5-1.6(1H,m), 2.1-2.3(1H,dd), 2.3-2.5(1H,dd), 3.5(2H,s), 4.0(1H,m), 4.2(1H,m), 6.9-7.1(2H,m), 7.3-7.4(4H,m), 7.7(2H,d), 7.9(1H,t), 8.1(1H,d), 10.54(1H,b)	Ib	A(ii)	12a	29	2-Anilino-6-[2-carboxy-1-(methyl)ethylaminocarbonyl(S-(2-methylpropyl))methylaminocarbonylmethyl]benzoxazole
20		644		0.75,(d),3H;0.8,(d),3H;1.35,(m),2H;1.4,(m),1H;2.1,(s),6H;2.35,(m),2H;2.7,(m),2H;3.5(m),2H;3.95,(m)2H;4.3,(m),1H;5.1,(m),1H;5.95,(m),2H;6.7-6.85,(m),3H;7.0,(t),1H;7.1,(d),1H;7.4-7.5(m),4H;7.75(d),2H;8.15,(d),1H;8.4,(d),1H;10.55,(s),1H.	no final stage	A(i)	12a	14, 30	2-Anilino 6-[2-(2,2-dimethylaminoethoxycarbonyl)1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
21		566		3.4(m,3H),3.6(s,2H),4.0(m,2H),5.95(s,2H),6.8(m,4H),7.0(m,2H),7.2(m,1H),7.4(m,6H),7.8(m,2H),10.0(s,1H),10.55(m,1H)	Ib	A(ii)	12a	4b, 5a	2-Anilino-6-{3-[2-S-methyl-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
22	460			2.35,(m),2H;3.7,(s),2H;3.85(m),2H;4.15,(m),1H;6.6,(d)1H;7.0,(t),1H;7.05-7,25(m),3H;7.3-7.5,(m),5H;7.7(d),2H;10.1,(s)1H;10.6,(s)1H.	Ia	A(i)	12a	5a, 9	2-Anilino-6-{3-[2-hydroxy-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
23	458	460		1.9(m),2H;2.35(t),2H;3.55(s),3H;3.65(s),2H;3.9(t),2H;6.6(d)1H;7.05-7.55(m),11H;10.05(s),1H.	Ia	A(i)	10	4b, 5a	2-(N-methylanilino)-6-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzoxazole

24	534	536		1.0(d),3H;2.1-2.5,(m),3H;3.65-3.85(m),5H;3.95(s),3H;4.7(s),2H;6.7,(d),1H;6.85-6.95(m),2H;7.0,(t),1H7.2(d),1H;7.3-7.4,(m),3H;7.7(d),2H;9.85,(s),1H;10.4(s),1H;12.1,(brs),1H.	Ia	A(i)	20	4b, 5a, 6a	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-methoxyanilinocarbonylmethoxy}benzoxazole
25	490	492		1.9(m),2H;2.38(t),2H;3.9-4.0,(m),5H;4.7,(s),2H;6.7-6.8,(m),2H;6.9,(d)1H;7.0,(t),1H;7.2,(d),2H;7.3-7.4,(m),3H;7.75,(d),2H;9.95(s),1H10.4,(s),1H;12.1(brs),1H.	Ia	A(i)	20	4b, 5a	2-Anilino-4-methoxy-6-{3-[3-carboxypropoxy]anilinocarbonylmethoxy}benzoxazole
26	474	476		1.9(m),2H;2.35(t),2H;3.55(s),2H;3.8-4.0(m),5H;6.6(d)1H;7.0-7.15(m),4H;7.2-7.4,(m),3H;7.7,(d),2H;10.05(s),1H;10.5,(s)1H.	Ia	A(i)	11	4b, 5a	2-Anilino-4-methoxy-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
27	521	522.5		2.55-2.90 (2H, m), 3.45 (1H, m), 3.65 (2H, s), 4.05 (2H, m), 6.55 (1H, d), 6.95-7.45 (14H, m), 7.75 (2H, d), 10.05 (1H, s), 10.55 (1H,s)	IIIa	A(ii)	12a	1, 4a,5a	2-Anilino-6-{3-[2-phenyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
28	601			0.75,(d),3H;0.85,(d),3H;1.4,(m),2H;1.5,(m),1H;2.65,(m),2H;3.5,(m)2H;3.95,(m),3H;4.3,(m),1H;5.1,(m),1H;5.95,(m),2H;6.7-6.85,(m),4H;7.0,(m),2H;7.4(t),2H;7.75(d),2H;8.15,(d),1H;8.4,(d),1H;10.5,(s),1H;12.2,(s)1H.	Ia	A(i)	11	29	2-anilino-4-methoxy-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
29	601			0.75,(d),3H;0.85,(d),3H;1.35,(m),2H;1.45,(m),1H;2.65,(m),2H;3.5,(m)2H;3.85,(m),3H;4.3,(m),1H;5.05,(m),1H;5.95,(m),2H;6.7,(m),1H;6.8,(m),2H;6.95-7.1,(m),4H;7.25-7.35,(m),2H;8.15,(m),2H;8.4,(d),1H;9.6,(m),1H;12.2,(s)1H.	Ia	A(i)	12a	29	2-(2-methoxyanilino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

30		476		1.9(m),2H;2.35(t),2H;3.65(s),2H;3.85,(s),3H;3.9,(t),2H;6.7(m)1H;6.95-7.4,(m),5H;7.3,(t),2H;7.4,(s),1H;8.15,(d),1H;9.6(s),1H 10.1,(s)1H.	Ia	A(i)	12a	4b, 5a	2-(2-Methoxyanilino)-6-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
31	585			0.8(6H,dd), 1.1(6H,d), 1.3-1.6(3H,m), 2.4-2.6(2H,m), 3.5(2H,s), 4.2(1H,m), 4.4(1H,m), 5.0(1H,m), 6.8(2H,d), 6.9-7.2(4H,m), 7.3-7.5(4H,m), 7.8(2H,d), 8.2(1H,d), 8.9(1H,b)		A(ii)	12a	29	2-Anilino-6-[2-carboxy-1-(4-isopropoxyphenyl)ethyl aminocarbonyl(S-(2-methylpropyl))methyla minocarbonylmethyl]benzoxazole
32	518	520		1.0(d),3H;2.1-2.4,(m),3H;3.65(s),2H;3.7-3.85(m),5H;6.8-6.95,(m),2H;7.0-7.2,(m),3H;7.35-7.45,(m),3H;7.8(d),2H;10.0,(s),1H;10.5(s),1H.	Ia	A(i)	11	4b, 5a, 6a	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-methoxyanilinocarbonyl methyl}benzoxazole
33	587	589		0.7,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.6,(m),2H;3.5d(q),2H;4.3,(q),1H;5.05,(q),1H;5.95,(d),2H;6.7-6.85,(m),3H;7.0,(t),1H;7.2,(d),1H;7.35(t),2H;7.5d(d),1H;7.65,(s),1H;7.75,(d),2H;8.15,(d),1H;8.4,(d),1H;10.35,(s),1H.	Ia	A(i)	23	29	2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylam inocarbonylmethyl]benz othiazole
34		462		1.9(m),2H;2.35(t),2H;3.7(s),2H;3.9,(t),2H;6.6(d)1H;7.0,(t)1H;7.05-7.2,(m),3H;7.25-7.4,(m),4H;7.5,(d),1H;7.7-7.8,(m),3H;10.1,(s),1H.	Ia	A(i)	23	4b, 5a	2-Anilino-6-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzot hiazole
35		587		0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.5-2.7(m),2H;3.5-3.6(m),2H;3.55(s),3H;4.25(m),1H;5.05(m),1H;5.95(s),2H;6.7-6.9(m),3H;7.1(d),1H;7.25-7.3(m).3H;7.4-7.55(m),4H;8.15(d),1H;8.4(d),1H.	Ia	A(i)	10	29	2-(N-methylanilino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylam inocarbonylmethyl]benz oxazole

36		591		0.75,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.6,(m),2H;3.55,(m)2H;4.3,(m),1H;5.1,(m),1H;5.95,(m),2H;6.7-6.85,(m),3H;7.0-7.1,(m),2H;7.25,(s),1H;7.4(t),2H;7.75(d),2H;8.2,(d),1H;8.4,(d),1H;10.7,(s),1H.	Ia	A(i)	12b	29	2-anilino-4-fluoro-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]-benzoxazole
37		464		1.9(m),2H;2.35(t),2H;3.7(s),2H;3.9(t),2H;6.6(d),1H;7.0-7.2(m),4H;7.25-7.45,(m),4H;7.75(d),2H;10.1(s),1H;10.75,(s),1H.	Ia	A(i)	12b	4b, 5a	2-Anilino-4-fluoro-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
38	617			0.75,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.5,(s),3H;2.6,(m),2H;3.5,(m)2H;4.3,(m),1H;5.05,(m),1H;5.95,(m),2H;6.7-6.85,(m),3H;7.0-7.1,(m),2H;7.2,(m),1H;7.35(t),2H;7.7(d),2H;8.15,(d),1H;8.35,(d),1H;10.6,(s),1H.	Ia	B	16	29	2-anilino-4-methylthio-6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
39	649			0.75,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.6,(m),2H;3.4,(s),3H;3.6,(m)2H;4.3,(m),1H;5.05,(m),1H;5.95,(m),2H;6.65-7.0,(m),3H;7.1,(m),1H;7.4,(t),2H;7.6(s),1H;7.75(m),3H;8.25,(d),1H;8.4,(d),1H;11.05,(s),1H.	Method 17				2-anilino-4-methylsulphonyl-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
40		598.4		0.77(6H,dd);1.36(2H,m);1.43 (1H,M);2.61(2H,t);3.54 (2H,t);4.28(1H,q);5.05 (1H,q);5.94(2H,s);6.70 (1H,d);6.80(2H,m);7.12(1H,d);7.41(1H,d);7.46(1H,d);7.57(1H,t);7.94(1H,d);8.15 (1H,d); 8.22(1H,s);8.35 (1H,d);10.99(1H,s);12.18(1H,s).	Ib	B		29	2-(3-Cyanophenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
41		460		1.9(m),2H;2.35(t),2H;3.15,(s)3H;3.7(m),2H;3.95(t),2H;6.8-7.05,(m)4H7.1,(m),1H;7.25-7.4,(m),4H;7.75,(d),2H;10.5(s),1H.	Ia	A(iii)	12a	13	2-Anilino-6-{3-[3-carboxypropoxy](N-methylanilino)carbonylmethyl}benzoxazole

42	589			1.75,(m)2H;1.9,(s),3H;2.25,(t),2H;2.6.(m)2H;3.55(m)2H;4.3,(m)1H;5.05,(m),1H;5.95,(s),2H;6.65-6.85,(m),3H;7.0,(t)1H;7.1,(d),1H;7.3-7.45,(m),4H;7.75(d),2H;8.25,(d),1H;8.45,(d),1H;10.55,(s),1H	Ia	A(i)	12a	30	2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylthioethyl)methylaminocarbonylmethyl]benzoxazole
43	621			1.9,(m)2H;2.65,(m),2H;2.8-3.0.(m)5H;3.55(m)2H;4.35,(m)1H;5.05,(m),1h;5.95,(s),2H;6.65-6.85,(m),3H;7.0,(t)1H;7.1,(d),1H;7.3-7.45,(m),4H;7.7(d),2H;8.2,(d),1H;8.45,(d),1H;10.55,(s),1H	Method 18				2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylsulphonylethyl)methylaminocarbonylmethyl]benzoxazole
44	615			0.75,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.55,(m),2H;3.4-3.55,(m)5H;3.85,(m),3H;4.25,(m),1H;5.0,(m),1H;5.95,(m),2H;6.65-6.85,(m),4H;6.9,(s),1H;7.25(t),1H;7.4-7.5(m),4H;8.1,(d),1H;8.6,(m),1H.	Ia	Method 19			2-N-methylanilino-4-methoxy-6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
45	469			2.0(m,2H),2.4(m,2H),4.2(m,4H),7.1(m,2H),7.4(m,5H),7.8(m,3H),8.0(m,2H),10.55(m,1H)	Ib	A(ii)	12a	4b, 5c	2-Anilino-6-{3-[3-carboxypropoxy]-4-cyanoanilinocarbonylmethyl}benzoxazole
46	639.1				Ib	B		29	2-(3,4-Dichlorophenylamino)-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
47					Ib	B		29	2-(4-Cyanophenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

48	613.5				Ib	B		29	2-(4-Acetylphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
49	619.2				Ib	B		29	2-(2-Chloro-6-methylphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
50	613.3				Ib	B		29	2-(3-Acetylphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
51		633			Ib	B		29	2-(2,5-Dimethoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
52		603			Ib	B		29	2-(4-Methoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
53	639.1				Ib	B		29	2-(2-Trifluoromethylphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

54	655.2				Ib	B		29	2-(4-Trifluoromethoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
55	663.4				Ib	B		29	2-(4-Phenoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
56	617.3				Ib	B		29	2-(3-Methylthiophenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
57	661.1				Ib	B		29	2-(3,4,5-Trimethoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
58	631.2				Ib	B		29	2-(2,6-Dimethoxyphenyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
59	599.2				Ib	B		29	2-(2-Ethylphenyl)amino6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

60		601.4			Ib	B		29	2-(2,6-Dimethylphenyl)-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
61	535			2.35 (3H, s), 2.50-2.80 (2H, m), 3.65 (2H, s), 3.70-3.80 (1H, m), 3.95-4.05 (2H, m), 6.60 (1H, d), 6.95-7.45 (13H, m), 7.75 (2H, d), 10.10 (1H, s), 10.55 (1H, s)	IIIa	A(ii)	12a	1, 4a,5a	2-Anilino-6-{3-[2-(2-methylphenyl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
62	589	590.7		2.60-2.85 (2H, m), 3.40-3.60 (1H, m), 3.65 (2H, s), 4.05 (2H, d), 6.60 (1H, d), 6.95-7.65 (12H, m), 7.75 (2H, d), 10.10 (1H, s), 10.55 (1H, s)	IIIa	A(ii)	12a	1, 4a,5b	2-Anilino-6-{3-[2-(3,4-dichlorophenyl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
63			488 (M-Br)	1.0 (m,3H), 2.2(m,2H), 2.4(m,1H), 3.6(s,2H), 3.8(d,2H), 4.0(s,3H), 6.6(d,1H), 6.8(s,1H), 7.1(m,3H),7.4(m,3H),7.75(d,2H), 10.1(m,1H), 10.5(m,1H).	Ib	A(ii)	11	4b, 5b, 6b	2-Anilino-4-methoxy-6-{4-bromo-3-[2-methyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
64		494		1.0 (m,3H), 2.05(m,1H), 2.1(m,1H), 2.4(m,1H), 3.8(m,4H), 6.75(m,1H), 7.0(m,1H), 7.2(d,1H), 7.4(m,5H),7.45(s,1H), 7.75(d,2H), 9.2(s,1H), 10.56(m,1H)	Ib	A(ii)	12a	4b, 5b, 6b	2-Anilino-4-methoxy-6-{6-chloro-3-[2-methyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
65		490		1.0 (m,3H), 2.05(m,2H), 2.1(m,2H), 2.4(m,1H), 3.7(s,3H), 4.8(d,2H), 6.1(d,1H), 6.8(m,2H), 7.0(m,1H), 7.2(m,1H), 7.35(m,3H),7.45(s,1H), 7.75(d,2H), 10.16(m,1H).	Ib	A(ii)	12a	4b, 5b, 6b	2-Anilino-6-{5-methoxy-3-[2-methyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole

66		458		1.5-1.8(4H,m), 2.2-2.3(2H,t), 3.7(2H,s), 3.9(2H,t), 6.6(1H,d), 7.0(1H,t), 7.1-7.4(7H,m), 7.5(1H,s), 7.8(2H,d), 10.1(1H,b), 10.55(1H,b)	Ib	A(ii)	12a	4b, 5a	2-Anilino-6-{3-[3-carboxybutoxy]anilinocarbonylmethyl}benzoxazole
67	486			0.9(6H,m), 1.8-1.9(1H,m), 2.0-2.2(1H,m), 2.2-2.4(2H,m), 3.7(2H,s), 3.8-3.9(2H,m), 6.6(1H,d), 7.0(1H,t), 7.1-7.2(3H,m), 7.2-7.4(4H,m), 7.8(2H,d), 10.1(1H,b), 10.55(1H,b)	IIIa	A(ii)	12a	1,4a,5a	2-Anilino-6-{3-[(R)-2-isopropyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
68		542.60	+Na	1.90 (2H, m), 2.40 (2H, t), 3.30 (3H,s), 3.65 (2H, s), 3.90 (2H, t), 4.00 (2H, t), 6.90 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.35 (4H, m), 7.45 (1H, s), 7.75 (2H, d), 10.10 (1H, s), 10.65 (1H, s)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-methoxyethoxy)-anilinocarbonylmethyl} benzoxazole
69		573.70		1.30 (2H, m), 1.45 (4H, m), 1.85 (2H, m), 2.15 (2H, t), 2.40 (4H, m), 2.60 (2H, t), 3.65 (2H, s), 3.90 (2H, t), 3.95 (2H, t), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.25 (1H, d), 7.30 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.05 (1H, brs)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
70		575.40		1.90 (2H, m), 2.30 (2H, t), 2.65 (6H, m), 3.60 (4H, m), 3.70 (2H, s), 3.90 (2H, t), 4.00 (2H, t), 6.90 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, s)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-N-morpholinylethoxy)-anilinocarbonylmethyl} benzoxazole
71		587.60		1.35 (2H, m), 1.50 (4H, m), 1.80 (4H, m), 2.20 (2H, t), 2.35 (6H, m), 3.65 (2H, s), 3.90 (4H, m), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.20 (1H, dd), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, s), 10.60 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N-piperidinylpropoxy)-anilinocarbonylmethyl} benzoxazole

72		589.6		1.70 (2H, m), 1.90 (2H, m), 2.10 (2H, t), 2.60 (6H, m), 3.20 (6H, s), 3.35 (4H, t), 3.65 (2H, s), 3.90 (4H, m), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.25 (1H, s), 7.35 (3H, m), 7.40 (1H, s), 7.75 (2H, d), 10.05 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-(bis-(N-methoxyethyl)amino)propoxy)-anilinocarbonylmethyl} benzoxazole
73		588.60		1.85 (4H, m), 2.10 (2H, t), 2.30 (4H, m), 2.35 (2H, t), 2.65 (4H, m), 3.65 (2H, s), 3.90 (4H, m), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N-piperazinylpropoxy)-anilinocarbonylmethyl} benzoxazole
74		602.60		1.80 (4H, m), 2.10 (3H, s), 2.30 (12H, m), 3.65 (2H, s), 3.90 (4H, m), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N,N'-methylpiperazinylpropoxy)-anilinocarbonylmethyl} benzoxazole
75		635.6		1.85 (4H, m), 2.15 (2H, t), 2.30 (4H, m), 2.40 (2H, t), 3.55 (4H, m), 3.65 (2H, s), 3.90 (4H, m), 6.95 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N-morpholinylpropoxy)-anilinocarbonylmethyl} benzoxazole
76		577.50		1.80 (2H, m), 1.90 (2H, m), 2.15 (2H, t), 2.65 (4H, m), 3.20 (3H, s), 3.35 (2H, t), 3.65 (2H, s), 3.90 (4H, m), 6.80 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.25 (1H, d), 7.30 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.10 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-(2-methoxyethylamino)propoxy)-anilinocarbonylmethyl} benzoxazole
77		547.50		1.80 (4H, m), 2.10 (8H, m), 2.30 (2H, t), 3.60 (2H, s), 3.90 (4H, m), 6.80 (1H, d), 7.00 (1H, t), 7.15 (2H, m), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.05 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-dimethylaminopropoxy)-anilinocarbonylmethyl} benzoxazole

78		573.60		1.65 (4H, m), 1.80 (4H, m), 2.05 (2H, t), 2.40 (4H, m), 3.65 (2H, s), 3.90 (4H, m), 6.80 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.05 (1H, s)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-N-pyrrolidinylpropoxy)-anilinocarbonylmethyl} benzoxazole
79		603.00		1.4(m,2H), 1.8(m,4H), 2.0(m,2H), 2.4(m,2H), 3.05(m,2H), 3.6(m,6H), 4.0(m,5H), 4.4(m,2H), 6.95(s,1H), 7.05(m,2H) 7.1(m,2H), 7.4(m,3H), 7.8(d,2H), 10.0(m,1H), 10.18(m,1H), 10.58(m,1H)	Ib	A(i)	11	26A	2-Anilino-4-methoxy-6-{3-[3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
80		570.50		1.90 (2H, m), 2.15 (2H, m), 2.40 (2H, t), 3.70 (2H, s), 3.85 (2H, t), 3.90 (2H, t), 4.20 (2H, t), 6.85 (1H, d), 7.05 (3H, m), 7.15 (1H, d), 7.35 (6H, m), 7.70 (2H, d), 7.90 (1H, s), 10.00 (1H, brs), 10.55 (1H, brs)	Ib	A(ii)	12a	25	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(3-N-imidazolylpropoxy)-anilinocarbonylmethyl} benzoxazole
81		575.40	+Na	1.90 (2H, m), 2.35 (2H, t), 3.65 (2H, s), 3.95 (2H, t), 5.10 (2H, s), 6.90 (1H, s), 7.00 (2H, m), 7.15 (1H, d), 7.40 (7H, m), 7.75 (3H, m), 8.50 (1H, d), 10.00 (1H, s)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(pyrid-2-ylmethoxy)-anilinocarbonylmethyl} benzoxazole
82		575.20	+Na	1.90 (2H, m), 2.30 (2H, t), 3.65 (2H, s), 3.90 (2H, t), 5.05 (2H, s), 7.00 (4H, m), 7.35 (6H, m), 7.75 (2H, d), 7.80 (1H, d), 8.50 (1H, d), 8.60 (1H, d), 10.05 (1H, s)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(pyrid-3-ylmethoxy)-anilinocarbonylmethyl} benzoxazole
83		553.50		1.90 (2H, m), 2.20 (2H, t), 3.65 (2H, s), 3.95 (2H, t), 5.10 (2H, s), 6.90 (1H, s), 7.10 (2H, m), 7.15 (1H, d), 7.35 (7H, m), 7.75 (2H, d), 8.55 (2H, d), 10.05 (1H, s)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(pyrid-4-ylmethoxy)-anilinocarbonylmethyl} benzoxazole

84	585.6			1.00 (3H, d), 1.35 (2H, m), 1.50 (4H, m), 2.15-2.45 (7H, m), 2.70 (2H, m), 3.65 (3H, m), 3.80 (1H, dd), 4.00 (2H, t), 6.85 (1H, d), 7.00 (2H, m), 7.15 (1H, d), 7.25 (1H, m), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 9.95 (1H, brs), 10.55 (1H, brs)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
85		no value		0.95 (3H, d), 1.35 (2H, m), 1.45 (4H, m), 1.95 (1H, dd), 2.20 (2H, m), 2.40 (4H, m), 2.60 (2H, m), 3.60 (3H, m), 3.80 (1H, dd), 3.95 (5H, m), 6.80 (2H, d), 7.00 (1H, t), 7.10 (2H, m), 7.25 (1H, m), 7.35 (2H, m), 7.75 (2H, d), 10.05 (1H, s)	Ib	A(i)	11	26A	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
86		693.60		1.35 (2H, m), 1.45 (4H, m), 2.25-2.40 (6H, m), 2.60 (2H, m), 3.35 (1H, m), 3.65 (2H, s), 3.90 (4H, m), 5.9 (2H, s), 6.75 (2H, s), 6.80 (1H, d), 6.90 (1H, s), 7.00 (2H, m), 7.15 (1H, d), 7.20 (1H, m), 7.35 (3H, m), 7.40 (1H, s), 7.75 (2H, d), 9.95 (1H, s)	Ib	A(i)	12a	26B	2-Anilino-6-{3-[2-(benzo[1,3]dioxoly-5-yl)-3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
87		723.60		1.35 (2H, m), 1.45 (4H, m), 2.40 (6H, m), 6.55 (2H, m), 3.55 (1H, m), 3.60 (2H, s), 3.90 (2H, t), 3.95 (5H, m), 5.90 (2H, s), 6.75 (2H, s), 6.80 (2H, m), 6.90 (1H, s), 7.00 (2H, m), 7.20 (1H, m), 7.35 (2H, m), 7.75 (2H, d), 9.95 (1H, s), 10.50 (1H, s)	Ib	A(i)	11	26B	2-Anilino-4-methoxy-6-{3-[2-(benzo[1,3]dioxoly-5-yl)-3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
88		559.70		1.65 (4H, m), 1.90 (2H, m), 2.10 (2H, t), 2.75 (2H, t), 3.65 (2H, s), 3.90 (2H, t), 3.95 (2H, t), 6.85 (1H, d), 7.00 (1H, t), 7.05 (1H, dd), 7.15 (1H, dd), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, brs)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-N-pyrrolidinylethoxy)-anilinocarbonylmethyl} benzoxazole
89		533.70		1.90 (2H, m), 2.15 (2H, t), 2.20 (6H, s), 2.55 (2H, t), 3.65 (2H, s), 3.85 (2H, t), 3.95 (2H, t), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, dd), 7.25 (1H, d), 7.35 (3H, m), 7.40 (1H, s), 7.70 (2H, d), 10.05 (1H, brs)	Ib	A(i)	12a	26A	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-dimethylaminoethoxy)-anilinocarbonylmethyl} benzoxazole

90		no value		1.95(m,2H), 2.05(m,2H), 2.4(m,2H), 3.65(m,4H), 3.9(m,2H), 7.0(m,2H), 7.2(d,2H), 7.4(m,5H), 7.6(m,2H), 7.75(d,2H), 10.02(m,1H), 10.55(m,1H)	Ib	A(i)	12a	27	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(N-morpholinylmethyl)-anilinocarbonylmethyl} benzoxazole
91		621.4		1.90 (2H, m), 2.20 (2H, t), 2.70 (4H, t), 2.85 (2H, t), 3.20 (6H, s), 3.40 (4H, t), 3.65 (2H, s), 3.90 (4H, m), 6.85 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.00 (1H, brs).	Ib	A(i)	12a	28,5a	2-Anilino-6-{3-[3-carboxypropoxy]-4-(3-(bis-(2-methoxyethyl)amino)ethoxy)-anilinocarbonylmethyl} benzoxazole
92		602.9		0.95 (3H, d), 1.80 (3H, m), 2.10 (1H, dd), 2.30 (5H, m), 2.40 (2H, t), 3.60 (7H, m), 3.85 (1H, m), 3.90 (2H, t), 6.80 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.10 (1H, brs).	Ib	A(ii)	12a	25	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-morpholinylpropoxy)-anilinocarbonylmethyl} benzoxazole
93		600.9		0.95 (3H, d), 1.35 (2H, m), 1.45 (4H, m), 1.80 (3H, m), 2.05 (1H, dd), 2.30 (7H, m), 3.60 (1H, m), 3.65 (2H, s), 3.90 (3H, m), 6.80 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.10 (	Ib	A(ii)	12a	25	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-piperidinylpropoxy)-anilinocarbonylmethyl} benzoxazole
94		583.9		1.0 (3H, d), 1.95 (1H, dd), 2.20 (4H, m), 3.65 (3H, m), 3.85 (3H, m), 4.15 (2H, t), 6.85 (2H, m), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (2H, m), 7.25 (1H, d), 7.35 (3H, m), 7.45 (1H, s), 7.60 (2H, d), 7.75 (2H, d), 10.05 (1H, brs).	Ib	A(ii)	12a	25	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(3-N-imidazolylpropoxy)-anilinocarbonylmethyl} benzoxazole
95		555.9		1.90 (2H, m), 2.20 (2H, t), 3.65 (2H, s), 3.90 (2H, t), 4.15 (2H, t), 4.30 (2H, t), 6.80 (1H, d), 6.85 (1H, s), 7.00 (1H, t), 7.10 (1H, d), 7.15 (1H, d), 7.25 (1H, s), 7.30 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.65 (1H, s), 7.75 (2H, d), 10.15 (1H	Ib	A(ii)	12a	28, 5a	2-Anilino-6-{3-[3-carboxypropoxy]-4-(2-N-imidazolylethoxy)-anilinocarbonylmethyl} benzoxazole

96		617.0		0.95 (3H, d), 1.35 (2H, m), 1.50 (4H, m), 1.95 (1H, dd), 2.25 (2H, m), 2.40 (4H, m), 2.60 (2H, t), 3.65 (3H, m), 3.80 (1H, m), 4.00 (5H, m), 6.80 (2H, m), 7.00 (1H, t), 7.10 (2H, m), 7.25 (1H, s), 7.35 (2H, m), 7.75 (2H, d), 10.10 (1h, brs), 10.55	Ib	A(ii)	11	28, 5a	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-piperidinylethoxy)-anilinocarbonylmethyl} benzoxazole
97		603.0		0.95 (3H, d), 1.70 (4H, m), 1.90 (1H, dd), 2.10 (1H, dd), 2.30 (1H, m), 2.75 (2H, m), 3.65 (3H, m), 3.80 (1H, m), 4.00 (5H, m), 6.80 (2H, m), 7.00 (1H, t), 7.10 (2H, m), 7.30 (1H, s), 7.35 (2H, m), 7.75 (2H, d), 10.10 (1H, brs), 10.60 (1H, brs).	Ib	A(ii)	11	28, 5a	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-pyrrolindinylethoxy)-anilinocarbonylmethyl} benzoxazole
98		573.0		0.95 (3H, d), 1.65 (4H, m), 1.95 (1H, dd), 2.10 (1H, dd), 2.30 (1H, m), 2.70 (2H, m), 3.65 (3H, m), 3.80 (1H, m), 3.95 (2H, t), 6.80 (1H, d), 7.00 (1H, t), 7.10 (1H, dd), 7.15 (1H, d), 7.25 (1H, s), 7.35 (3H, m), 7.45 (1H, s), 7.75 (2H, d), 10.15	Ib	A(ii)	12a	28, 5a	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(2-N-pyrrolindinylethoxy)-anilinocarbonylmethyl} benzoxazole
99		597.3		1.00 (3H, d), 2.05 (1H, dd), 2.30 (2H, m), 3.65 (2H, s), 3.75 (1H, dd), 3.85 (1H, dd), 3.95 (3H, s), 5.10 (2H, s), 6.80 (1H, s), 6.90 (1H, d), 7.00 (1H, t), 7.10 (2H, m), 7.35 (5H, m), 7.75 (2H, d), 8.55 (2H, d), 10.10 (1H, brs).	Ib	A(ii)	11	28, 5c	2-Anilino-4-methoxy-6-{3-[2-methyl-3-carboxypropoxy]-4-(pyrid-4-ylmethoxy)-anilinocarbonylmethyl} benzoxazole
100		567.3		1.00 (3H, d), 2.15 (1H, dd), 2.30 (2H, m), 3.65 (2H, s), 3.80 (2H, m), 5.30 (2H, s), 7.00 (2H, m), 7.10 (1H, d), 7.15 (1H, d), 7.35 (5H, m), 7.75 (2H, d), 7.85 (2H, d), 8.80 (2H, d), 10.10 (1H, brs), 10.55 (1H, brs).	Ib	A(ii)	12a	28, 5c	2-Anilino-6-{3-[2-methyl-3-carboxypropoxy]-4-(pyrid-4-ylmethoxy)-anilinocarbonylmethyl} benzoxazole
101		587		0.6(d) and 0.7(d), 3H; 0.85(m),3H; 1.2-1.6(m), 6H; 2.4-2.8(m), 2H; 3.9(q),1H; 4.25(m),1H; 4.95(q) and 5.05(q),1H; 5.95(m), 2H; 6.6- 6.75(m), 2H; 6.8(m),1H; 7.0(t),1H; 7.15(m),1H; 7.3-7.45(m),4H; 7.75 (m), 2H; 8.0(m),1H; 8.15(d) and 8.35(d),1H; 10.	Ia	A(i)	12c	29	2-anilino 6-[1-{2-Carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonyl} ethyl] benzoxazole.

102		460		1.4(d),3H; 1.9(m),2H; 2.35(t),2H; 3.8-3.95(m),3H; 6.8(d), 1H; 7.0(t),1H;7.05-	Ia	A(i)	12c	4b, 5a	2-Anilino-6-{1-(3-[3-carboxypropoxy]anilino carbonyl)ethyl)}benzoxazole
103		474		1.6(s),6H; 1.9(m),2H; 2.35(t),2H; 3.9(t),2H; 6.8(d), 1H; 7.0(t),1H;7.05-7.2(m),3H; 7.25(s)1H; 7.3-7.45(m),3H; 7.5 (m)1H; 7.75(d),2H; 9.0(s),H; 10.55(s),1H; 12.1(s)1H.	Ia	A(i)	12c	4b, 5a	2-Anilino-6-{2-(3-[3-carboxypropoxy]anilino carbonyl)prop-2-yl)}benzoxazole
104		601		0.75(m),6H; 1.2-1.6(m), 9H; 2.45(m), 2H; 4.3(m),1H; 5.05(q),1H; 5.95(m), 2H; 6.7(m),1H; 6.8(m),2H; 7.05(m),2H; 7.15(m),1H; 7.35(m),3H; 7.45(s),1H; 7.75 (d), 2H; 8.0(d),1H; 10.55(s),1H;12.2(s),1H.	Ia	A(i)	12c	29	2-anilino 6-[2-{2-Carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonyl}prop-2-yl]benzoxazole.
105	580			2.5-2.7(1H,dd), 2.7-2.9(1H,dd), 3.4(1H,m), 4.0(2H,d), 4.7(2H,s), 5.9(2H,s), 6.6(1H,m), 6.7-7.1(5H,m), 7.1-7.4(7H,m), 7.8(2H,d), 10.0(1H,b), 10.45(1H,b)	IIIa	A(ii)	A(ii)	20, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilino carbonylmethoxy}benzoxazole
106	564			2.5-2.7(1H,dd), 2.7-2.9(1H,dd), 3.4(1H,m), 3.7(2H,s), 4.0(2H,d), 5.9(2H,s), 6.6(1H,d), 6.7-6.8(2H,m), 6.9-7.2(5H,m), 7.2-7.5(5H,m), 7.9(2H,d), 10.08(1H,b), 10.45(1H,b)	IIIa	A(ii)	A(ii)	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole
107	470			2.2-2.6(2H,m), 2.9(1H,m), 3.7(2H,s), 3.9(2H,d), 5.1(2H,m), 5.8(1H,m), 6.6(1H,d), 6.9-7.2(4H,m), 7.2-7.5(5H,m), 7.8(2H,d), 10.1(1H.s), 10.6(1H,s)	Ib	A(ii)	A(ii)		2-Anilino-6-{3-[2-vinyl-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole.

108		566		3.4(m,3H),3.6(s,2H),4.0(m,2H),5.95(s,2H),6.8(m,4H),7.0(m,2H),7.2(m,1H),7.4(m,6H),7.8(m,2H),10.0(s,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{4-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
109	610			2.5-2.7(1H,dd), 2.7-2.9(1H,dd), 3.4(1H,m), 3.9(3H,m), 4.0(2H,d), 4.7(2H,s), 5.9(2H,s), 6.6-6.7(2H,m), 6.8-7.1(5H,m), 7.3-7.4(5H,m), 7.7(2H,d), 10.0(1H,s), 10.4(1H,s), 12.1(1H,s)	IIIa	A(ii)	11	1, 4a, 5a	2-Anilino-4-methoxy-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonylmethoxy}benzoxazole
110	608			1.2(t,3H),2.6(m,2H),2.8(m,1H),3.6(m,2H),3.9(m,2H),5.95(s,2H),6.8(m,2H),7.05(m,4H),7.4(m,5H),7.7(m,3H),10.0(s,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-4-ethoxyanilinocarbonylmethyl}benzoxazole
111	578			1.85(s,3H), 2.6(m,2H),2.8(m,1H),3.7(m,2H),4.0(m,2H), 5.95(s,2H),6.8(m,3H),7.0(m,5H), 7.4(m,4H),7.75(d,2H),9.4(s,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-2-methylanilinocarbonylmethyl}benzoxazole
112	594			2.6(m,2H),3.1(m,1H),3.6(m,5H),4.0(m,2H), 5.95(s,2H),6.8(m,3H),7.0(m,4H), 7.4(m,5H),7.75(d,2H),10.04(m,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-5-methoxyanilinocarbonylmethyl}benzoxazole
113	594			2.75(m,2H),3.6(m,1H),3.75(s,3H),3.8(m,2H), 3.95(m,2H), 5.95(s,2H),6.8(m,2H),6.9(m,2H),7.0(m,2H), 7.4(m,5H),7.8(m,2H),9.2(m,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-6-methoxyanilinocarbonylmethyl}benzoxazole

114	594	596		2.7,(m),2H;3.6,(m),1H;3.7,(m),2H;3.96,(s)3H;4.05,(m),2H;6.0(s),2H;6.65,(m),1H;6.75-6.9,(m),3H;6.95-7.25,(m)5H;7.3-7.65,(m),3H;7.75,(d),2H;10.1,(s)1H;10.5,(s),1H.	IIIa	A(ii)	11	1, 4a, 5a	2-Anilino-4-methoxy-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
115		596		2.6(m,1H),2.9(m,2H),3.6(m,5H),4.0(m,2H),5.95(s,2H),6.8(m,3H),7.0(m,3H),7.4(m,5H),7.75(d,2H),10.0(s,1H)	IIIa	A(ii)	12a	1, 4a, 5a	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-4-methoxyanilinocarbonylmethyl}benzoxazole
116	484	486		2.3-2.5(5H,m), 3.7(2H,s), 3.9(2H,d), 5.0(2H,m), 5.9(1H,m), 6.6(1H,d), 7.0-7.5(9H,m), 7.8(2H,d), 10.12(1H,b), 10.6(1H,b)	IIIb	A(ii)	12a	3, 4a, 5b	2-Anilino-6-{3-[2-allyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole.
117	484			2.1-2.5(5H,m), 3.7(2H,s), 3.9(2H,d), 5.0(2H,m), 5.9(1H,m), 6.6(1H,d), 7.0-7.5(9H,m), 7.8(2H,d), 10.1(1H,b), 10.55(1H,b)	IIIb	A(ii)	12a	3, 4a, 5b	2-Anilino-6-{3-[2-allyl-3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole.
118	566			2.95(m,2H),3.95(m,2H),4.0(m,2H),5.95(s,2H),6.8(m,2H),7.0(m,3H),7.2(m,2H),7.4(m,5H),7.7(d,2H),10.08(s,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a,5c	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-4-bromoanilinocarbonylmethyl}benzoxazole
119	598			2.8(m,1H),3.75(m,2H),4.0(m,2H),5.95(s,2H),6.8(m,2H),7.0(m,3H),7.2(m,2H),7.4(m,5H),7.7(d,2H),9.5(s,1H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a,5c	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-6-chloroanilinocarbonylmethyl}benzoxazole

120	633			2.7(m,2H),4.0(m,4H),5.95(s,2H),6.8(m,5H),7.0(m,2H),7.4(m,5H),7.75(d,2H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a,5c	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-5-trifluoromethylanilinocarbonylmethyl}benzoxazole
121	564			2.9(m,2H),3.25(m,1H),4.0(m,6H),5.95(s,2H),6.8(m,3H),7.0(m,4H),7.4(m,5H),7.7(d,2H),10.55(m,1H)	IIIa	A(ii)	12a	1, 4a,5c	2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]-4-chloroanilinocarbonylmethyl}benzoxazole
122		574		(DMSOd6) 0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.5-2.7(m),2H;3.5-3.6(m),2H;4.25(m),1H;5.05(m),1H;5.95(s),2H;6.7-6.9(m),3H;7.1(d),1H;7.3-7.45(m).3H;8.15(d),1H;8.2-8.3(m),2H;8.35(d),1H;8.85(s),1H;10.8(b),1H.	Ia	A(i)	12a	29	2-(3-pyridylamino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
123	0	447		(DMSOd6):1.9(m),2H;2.35(t),2H;3.7(s),2H;3.9(t),2H;6.6(d),1H;7.0-7.5(m),9H;8.25(m),2H;8.85(s),1H;10.08(s),1H.	Ia	A(i)	12a	4b, 5a	2-(3-pyridylamino)-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl}benzoxazole
124		590		(DMSOd6) 0.7-0.8(dd),6H;1.3-1.4(m),2H;1.4-1.5(m),1H;2.5-2.7(m),2H;3.5-3.6(m),2H;4.25(m),1H;5.05(m),1H;6.0(s),2H;6.65-6.9(m),3H;7.1(d),1H;7.35-7.5(m),3H;7.55(d),1H;7.9(d),1H;8.25(d),1H;8.45(d),1H;8.85(s),1H;11.1(s),1H;12.25(s)1H.	Method 15				2-[(N-oxidopyrid-3-yl)amino]- 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
125	588			DMSOd6:0.7,(d),3H;0.8,(d),3H;1.35,(m),2H;1.45,(m),1H;2.6,(m),2H;3.55(q),2H;4.3,(m),1H;5.05,(q),1H;5.95,(d),2H;6.65-6.85,(m),3H;7.2,(m),1H;7.35,(m),1H;7.5d(m),1H;7.65d(d),1H;8.15,(m),1H;8.2,(d),1H;8.2-8,4,(m),2H;8.85,(d),1H.	Ia	A(i)	12a	29	2-(Pyrid-3-ylamino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzothiazole

126	461			(DMSOd6):1.9(m),2H;2.35 (t),2H;3.7(s),2H;3.9,(t),2H; 6.6(d)1H;7.0-7.2,(m)2H;7.3,(m),2H;7.4,(m),1H;7.55,(d),1H;7.75,(s),1H:8.2,(d)1H;8.3,(m),1H;8.85,(d),1H.	Ia	A(i)	24	4b, 5a	2(-Pyrid-3-ylamino)-6-{3-[3-carboxypropoxy]anilino carbonylmethyl}benzothiazole
127	592			1.2(6H,s), 2.2-2.7(5H,m), 3.7(2H,s), 3.8(2H,d),4.5(1H,m), 6.6(1H,d), 6.8(2H,d), 6.9-7.5(11H,m), 7.8(2H,d), 10.05(1H,b),m 10.55(1H,b)	IIIa	A(ii)	12a	2, 5a	2-Anilino-6-{3-[2-(4-isoproxybenzyl)-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole.
128	527	529		1.2-1.4(2H,m), 1.4-1.7(3H,m), 2.1-2.3(3H,m), 2.5(2H,d), 3.0(2H,d), 3.7(2H,s), 3.9(2H,d), 6.6(1H,d), 6.9-7.5(9H,m), 7.9(2H,d), 10.1(1H,b), 10.54(1H,b)	IIIa	A(ii)	12a	2, 5a	2-Anilino-6-{3-[2-(4-piperidinyl)-3-carboxypropoxy]anilino carbonylmethyl}benzoxazole.
129	621.1			no nmr data	Ia	B	12a (Step 3)	29	2-(1-Naphthyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
130	620.9			no nmr data	Ia	B	12a (Step 3)	29	2-(2-Naphthyl)amino-6-[(S)-2-carboxy-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole
131	572	574		0.75(6H,dd), 1.3-1.55(3H,m), 2.6(2H,t), 3.55(2H,q), 4.3(1H,q), 5.05(1H,q), 5.95(2H,s), 6.65-7.0(3H,m), 7.15(1H,d), 7.35-7.45(2H,m), 7.5(2H,d), 8.15(1H,d)	Ia	C		29	2-(Pyrid-4-ylamino)-6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole

132	578			1.8(2H,m), 2.3-2.6(2H,m), 2.9(1H,m), 3.7(2H,s), 4.3(1H,m), 5.9(2H,s), 6.6(1H,d), 6.7-6.9(3H,m), 7.0(1H,t), 7.1-7.2(2H,m), 7.3-7.5(6H,m), 7.8(2H,d), 10.08(1H,b), 10.55(1H,b)	Ib	A(ii)	12a	5a, 7	2-Anilino-6-{3-[1-hydroxy-3-(benzo[1,3]dioxyol-5-yl)-4-carboxybutyl]anilinocarbonylmethyl}benzoxazole
133	576			2.4-2.7(2H,m), 3.2-3.4(2H,m), 3.6(1H,m), 3.9(2H,s), 5.9(2H,s), 6.7(2H,m), 6.9(1H,s), 7.0(1H,t), 7.2(1H,d), 7.3-7.5(5H,m), 7.6(1H,d), 7.7(2H,d), 7.8(1H,d), 8.1(1H,s), 10.3(1H,b), 10.55(1H,b)	Ib	A(ii)	12a	5b, 7	2-Anilino-6-{3-[1-oxo-3-(benzo[1,3]dioxyol-5-yl)-4-carboxybutyl]anilinocarbonylmethyl}benzoxazole
134	560			2.5-2.8(2H,m), 3.7(2H,s), 4.3(1H,m), 6.0(2H,s), 6.4(2H,m), 6.8-7.5(12H,m), 7.65(1H,s), 7.8(2H,d), 10.2(1H,s), 10.7(1H,s)	Ib	A(ii)	12a	5b, 7	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxy-(E)-but-1-enyl]anilinocarbonylmethyl}benzoxazole
135	606			2.4-2.7(2H,m), 3.2-3.6(3H,m), 3.7(2H,s), 3.9(3H,s), 5.9(2H,s), 6.7(2H,m), 6.8(1H,s), 6.9(1H,s), 7.0(1H,t), 7.1(1H,s), 7.3-7.5(3H,m), 7.6(1H,d), 7.7(2H,d), 7.8(1H,d), 8.1(1H,s), 10.3(1H,b), 10.5(1H,b)	Ib	A(ii)	11	5b, 7	2-Anilino-4-methoxy-6-{3-[1-oxo-3-(benzo[1,3]dioxyol-5-yl)-4-carboxybutyl]anilinocarbonylmethyl}benzoxazole
136		560		2.8-3.0(1H,dd), 3.1-3.2(1H,dd), 3.7(2H,s), 4.5(1H,m), 6.0(2H,s), 6.8(2H,m), 7.0(2H,m), 7.1-7.3(3H,m), 7.3-7.5(5H,m), 7.7(1H,s), 7.8(2H,d), 10.1(1H,b), 10.54(1H,b)	IV	A(ii)	12a	5b, 7a	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxybut-1-ynyl]anilinocarbonylmethyl}benzoxazole
137	562			1.7-1.9(2H,b), 2.1-2.3(2H,b),2.5-3.0(2H,m), 3.3(1H,m), 3.7(2H,s), 6.0(2H,s), 6.6(1H,m), 6.8(3H,m), 7.0(1H,t), 7.1-7.2(2H,m), 7.3-7.5(6H,m), 7.8(2H,d), 10.0(1H,b), 10.55(1H,b), 11.9(1H,b)	IV	A(ii)	12a	5a, 7a	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxybutyl]anilinocarbonylmethyl}benzoxazole

138	560			2.2-2.8(2H,m), 3.7(2H,s), 4.2(1H,m), 5.8(1H,t), 6.1(2H,s), 6.4(1H,d), 6.7-7.5(12H,m), 7.55(1H,s), 7.7(2H,d), 10.1(1H,b), 10.55(1H,b)	IV	A(ii)	12a	5b, 7a	2-Anilino-6-{3-[3-(benzo[1,3]dioxyol-5-yl)-4-carboxy-(Z)-but-1-enyl]anilinocarbonylmethyl}benzoxazole
139	440			2.3-2.7(4H,m), 3.7(2H,s), 6.1-6.4(2H,m), 7.0-7.1(2H,m), 7.1-7.5(7H,m), 7.6(1H,s), 7.8(2H,d), 10.1(1H,b), 10.55(1H,b)	IV	A(ii)	12a	5b, 7a	2-Anilino-6-{3-[4-carboxy-(E)-but-1-enyl]anilinocarbonylmethyl}benzoxazole

I) Final step

Ia Hydrolysis using NaOH

This is described in example 1 above.

Ib Hydrolysis using LiOH

Preparation of 2-Anilino-6-(3-[2-vinyl-3-carboxypropoxy]anilinocarbonyl methyl)benzoxazole (example107)

A solution of 2-anilino-6-(3-[2-vinyl-3-carbomethoxypropoxy]anilinocarbonyl methyl) benzoxazole(82mg) in a mixture of methanol(0.5mL) and THF (1.5mL) was treated with 1N LiOH(0.68mL) and water (4mL) and stirred for 4 hours. The organic solvents were removed by evaporation under reduced pressure and the solution was filtered through Celite then acidified with 2NHCl (0.34mL) to give a white precipitate which was collected by filtration, washed with water and dried at reduced pressure over phosphorous pentoxide to give product- (54mg).

II Hydrogenolysis of Acid protecting Group

Preparation of 2-Anilino 6-[2-Carboxy-1-([2,4-dimethylpent-3-yl]oxycarbonyl0 ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole (example 2)

This is described in example 8 above.

IIIa TFA Cleavage of a t-butyl ester

Preparation of 2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy]anilinocarbonyl methyl}benzoxazole (example 106)

2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-(carbo-t-butoxy)propoxy]anilino carbonylmethyl}benzoxazole(267mg) was treated with 90% (v/v) trifluoroacetic acid(3.0mL). The solution was stirred for 1 hour at ambient temperature. The trifluoroacetic acid was removed by distillation at reduced pressure and the residue was diluted with iced water(10mL). The precipitate was collected by filtration, washed with water and then ether. It was then dried at reduced pressure over phosphorous pentoxide to give product (210mg).

IIIb (alternative method of hydrolysing t-butyl esters)

Preparation of 2-anilino-6-(3-[2-(S)-allyl-3-{carboxy }propoxy]anilinocarbonylmethyl) benzoxazole (example 116)

Trimethylsilyltriflate(299ul) was added to a solution of 2-anilino-6-(3-[2-(s)-allyl-3-{carboxy-t-butoxy}propoxy]anilinocarbonylmethyl)benzoxazole(170mg) in dry dioxan containing triethylamine(236ul). The solution was warmed to 60°C for 30 min and the solvents were removed by evaporation under reduced pressure. The residue was then triturated with water to give product as an off white solid which was recovered by filtration.

IV Final Step as decarboxylation

Preparation of 2-Anilino-6-{3-[3-(benzo-1,3-dioxol-5-yl)-4-carboxybut-1-ynyl] anilino carbonylmethyl}benzoxazole (example 136)

A solution of 2-anilino-6-{3-[3-(benzo-1,3-dioxol-5-yl)-4,4-dicarboxybut-1-ynyl] anilinocarbonylmethyl}benzoxazole (330mg) in acetonitrile(20mL) containing copper(I) oxide was heated at reflux under argon for 6 hours. After removal of the acetonitrile under reduced pressure the solid residue was triturated with 0.1N HCl, filtered, washed with 0.1NHCl, water and then diethyl ether. It was then dried under reduced pressure over P_2O_5 to give product (200mg).

II Penultimate Stage

Method A(i)

This is described in example 1g above.

Method A(ii)

Preparation of 2-Anilino-6-{3-[2-(benzo[1,3]dioxyol-5-yl)-3-carboxypropoxy] anilinocarbonyl methoxy}benzoxazole (example 105)

A mixture of 2-anilino-6-carboxymethoxybenzoxazole (110mg, 0.39mmol) and methyl leucine-3-amino-3-(3,4-methylenedioxyphenyl)propionate (169mg, 0.5mmol) in DMF (5 mL) was treated sequentially with (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (222mg, 0.58 mmol) and diisopropylethylamine (269 mL). The mixture was stirred at room temperature overnight. The mixture was then partitioned between EtOAc and water. The EtOAc layer was separated, washed with 1M citric acid, saturated $NaHCO_3$ solution and concentrated in vacuo to a white solid. The solid was washed with water and ether to give product (235 mg, 100%) as a white solid.

HPLC Dynamax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 19.06 min.

MS 603 $(M+H)^{+1}$ H nmr (DMSOd6 0.9(6H,dd), 1.3-1.6(3H,m), 2.6-2.8(2H,m), 3.5(3H.s), 4.4(1H,m), 4.5(2H,s), 5.1(1H,m), 5.9(2H,s), 6.7-6.9(4H,m), 7.0(1H,t), 7.2(1H,s), 7.3-7.4(3H,m), 7.7(2H,d), 8.0(1H,d), 8.5(1H,d), 10.45(1H,b)

Method A(iii)

Preparation of 2-Anilino-6-{3-[3-methoxycarbonylpropoxy](N-methylanilino)carbonyl methyl}benzoxazole (example 41)

A mixture of 2-anilino-6-carboxymethylbenzoxazole(0.09g), dichloromethane(10mL) and thionyl chloride(0.2mL) was stirred at room temperature for 3h and then evaporated to dryness. A solution of the residue in tetrahydrofuran was added to a stirred mixture of methy-4-(N-methylaminophenoxy)butyrate(0.07g), triethylamine(0.1mL) and tetrahydrofuran(2mL) and the mixture was stirred at room temperature for 18h. Ethyl acetate(10mL) was added and the mixture washed successively with 1N hydrochloric acid, 1N sodium hydroxide and brine, dried and evaporated to dryness to give product (0.08g), [m/e474,MH+].

Method B

Preparation of 3-cyanophenylamino-6-[(S)2-methoxycarbonyl-1-(benzo[1,3]dioxyol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole (example 40)

A stirred solution of [(S) 2-methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-(3-cyanophenylureido)benzene (0.11g, 0.175mM) in THF at 5 °C was treated with $(n\text{-}Bu)_3P$ (65μL, 0,26mM) and ADDP(66mg, 0.26mM). After 10minutes, the mixture was warmed to room temperature and stirred for 18 hrs. The mixture was evaporated to dryness, the residue dissolved in EtOAc, washed with 1M citric acid, with saturated aqueous $NaHCO_3$ and then dried over $MgSO_4$ before being evaporated to give an oil. This was dissolved in CH_2Cl_2 and purified by chromatography on silica (eluting with 80% EtOAc/iso-hexane) to give product as a gum (10mg, 9.4%).

^1H NMR ($CDCl_3$, 300MHz): δ 0.88 (6H, m); 1.58 (2H,m); 1.69 (1H, m); 2.79 (2H, m); 3.46 (2H, t); 3.61 (3H, s); 4.52 (1H, m); 5.25 (1H, q); 5.91 (2H, s); 6.61 (1H, d); 6.70 (3H, m); 7.09 (1H, d); 7.15 (1H, s); 7.29 (1H, d); 7.35 (1H, d); 7.45 (1H,t); 7.63 (1H, t); 7.85 (1H, d); 8.04 (1H, d). MS (ES^+) m/z 612 (MH^+).

(a) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-nitrobenzene

A mixture of 3-hydroxy-4-nitrophenylacetic acid (4.10g, 12.2mM), [(S) 2-methoxycarbonyl-1(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)(2-methylpropyl)]methylamine (2.40g, 12.2 mM), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)(3.51g, 18.3 mM), hydroxybenzotriazole(HOBT)(2.8g, 18.3 mM) and N-methylmorpholine(NMM) (1.36ml, 12.2mM) in DMF (15ml) was stirred under an argon atmosphere for 20 hours at room temperature. The DMF was evaporated, the residue dissolved in EtOAc/water, the organic phase separated, washed with saturated aqueous $NaHCO_3$ and with brine. After drying over MgSO4, the solution was evaporated to give an oil which on triturating with Et_2O gave [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-

methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-nitrobenzene as a solid (4.47g, 71%).

H^1 NMR ($CDCl_3$, 300MHz) : δ 0.89 (6H,m); 1.59 (1H,m); 2.77 (2H,t); 3.59 (2H,s); 3.62 (3H,s); 4.45 (1H,m); 5.24 (1H,q); 5.92 (2H,s); 6.10 (1H,d); 6.72 (3H,m); 6.92 (1H,d); 7.00 (1H,d); 7.09 (1H,s); 8.07 (1H,d).

MS(ES^+) m/z 516 (MH^+).

(b) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-aminobenzene

A mixture of [(S) 2-methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-nitrobenzene (1g, 1.94mM), 10% Pd/C (300mg) and CH_2Cl_2 (25ml) was stirred vigorously under a hydrogen atmosphere for 2hrs, filtered, washed with CH_2Cl_2 and with MeOH and evaporated to dryness to give product as a glass (0.93g, 98.75%).

^1H MNR (DMSO, 300MHz): δ 0.74 (3H,d); 0.80 (3H,d); 1.29 (2H,m); 1.40 (1H,m); 2.69 (2H,m); 3.28 (2H,m); 3.49 (3H,s); 4.24 (1H,q); 5.07 (1H,q); 5.95 (2H,s); 6.41 (1H,d); 6.47 (1H,d); 6.55 (1H,s); 6.68 (1H,d); 6.79 (1H,d); 6.84 (1H,s); 7.82 (1H,d); 8.23 (1H,d).

MS (ES^+) m/z 486 (MH^+).

(c) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-(3-cyanophenylureido)benzene

A mixture of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-aminobenzene (243mg, 0.5mM), and 3-cyanophenylisocyanate (72mg, 0.5mM) in EtOAc (10ml) was heated at reflux for 20 hrs, cooled, treated with charcoal, filtered and evaporated to give a glass. This was then triturated with Et_2O and gave a solid which was purified on silica (eluting with 5% $MeOH/CH_2Cl_2$). Appropriate fractions were combined, evaporated and triturated with CH_2Cl_2 to give product as a solid (140mg, 44.5%).

^{1}H NMR (DMSO, 300MHz): δ 0.75 (3H,d); 0.81 (3H,d); 1.34 (2H,t); 1.44 (1H,m); 2.69 (2H,m); 3.31 (2H,q); 3.50 (3H,s); 4.27 (1H,q); 5.09 (1H,q); 6.63 (1H,d); 6.70 (1H,d); 6.76 (1H,s); 6.80 (1H,d); 6.84 (1H,d); 7.37(1H,d); 7.46 (1H,t); 7.58 (1H,d); 7.88 (1H,d); 7.96 (1H,s); 8.01 (1H,d); 8.16 (1H,s); 8.35 (1H,d); 9.57 (1H,s); 9.87 (1H,s).

MS (ES^+) m/z 630 (MH^+).

Method C

Preparation of 2-(pyrid-4-yl)amino-6-[2-methoxycarbonyl-1-(benzo[1,3]dioxoly-5-yl) ethyl aminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole (example 131)

A mixture of N-[4-{2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]}-2-hydroxyphenyl] N'- (pyrid-4-yl)urea(150mg), dichloromethane(1mL), tri-n-butylphosphine(130mg) and 1,1'-(azodicarbonyl) dipiperidine (160mg) was stirred at ambient temperature for 24h. The mixture was treated with water and ethyl acetate. The organic phase was separated, washed successively with water and brine, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of methanol and dichloromethane to give product (40mg), [m/e588,MH+].

(a) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-nitrobenzene

To a solution of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-hydroxy-4-nitrobenzene (0.515g, 1mM) in dry DMF (2 mL), tertiarybutyldimethylsilylchloride (TBDMSCl) (0.181g 1.2mM) and imidazole (0.136g, 2mM) were added. The mixture was stirred at ambient temperature for two days. Aqueous sodium bicarbonate was added, extracted with EtOAc, dried over $MgSO_4$ and then evaporated. The residue was purified by silica gel chromatography (eluting with 50% EtOAc/iso-hexane) and evaporating the appropriate fractions to give product as a crystalline solid (0.32g, yield= 51%).

^{1}H NMR($CDCl_3$, 300MHz) δ: 0.26(6H,s); 0.88(6H,q); 1.02(9H,s); 1.40- 1.66(3H,m); 2.78(2H,m); 3.52(2H,s); 3.63(3H,s); 4.44(1H,m); 5.24(1H,q); 5.93(2H,s); 5.96(1H,d); 6.72(3H,m); 6.96(3H,m); 7.80(1H,d)

$MS(ES^+)$ m/z 630 (MH^+)

(b) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-aminobenzene

A mixture of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-nitrobenzene (0.32g, 0.51mM), 10% Pd/C (0.5g) and CH_2Cl_2 (30mL) was stirred under a hydrogen atmosphere for 24 hr., filtered and evaporated to dryness to give product as an oily glass (0.22g, yield=72%).

^{1}H NMR ($CDCl_3$, 300MHz) δ: 0.25(6H,d); 0.85(6H,m); 1.01(9H,s); 1.42(2H,m); 1.59(1H,m); 2.76(2H,m); 3.47(2H,s); 3.62(3H,s); 4.41(1H,m); 5.21(1H,q); 5.93(2H,s); 6.62- 6.80(6H,m).

$MS(ES^+)$ m/z 600 (MH^+)

(c) Preparation of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-isocyanatobenzene

A stirred solution of [(S) 2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylamino carbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-aminobenzene (1g, 1.67mM) in CH_2Cl_2 was treated dropwise with a solution of triphosgene (165mg, 0.55mM) in CH_2Cl_2 (8mL) over half an hour. The mixture was stirred for a further half an hour and evaporated to dryness to give product as a glass (0.9g, yield =86%).

^{1}H NMR (CDCl3, 300MHz) δ: 0.24(6H,s): 0.88(6H,q); 0.93(9h,s); 1.34(1H,m); 1.40(1H,m); 1.51(1H,m); 2.69(2H,dq); 3.43(2H,s); 3.55(3H,s); 4.35(1H,q); 5.14(1H,q); 5.79(1H,d); 5.86(2H,s); 6.61- 6.73(5H,m); 6.90(1H,d); 7.00(1H,d).

C^{13},$CDCl_3$, ppm:-5.777, 16.878, 20.481, 21.144, 23.113, 24.063, 38.466, 39.221, 41.499, 48.152, 50.190, 75.055, 75.373, 75.691, 99.478, 105.253, 106.702, 117.857, 117.925,

120.676, 122.995, 123.332, 127.578, 130.995, 132.661, 145.412, 146.289, 148.880, 169.189, 169.397, 169.585.

MS(ES^+) m/z 626 (MH^+). IR Film N=C=O ,2245.9cm^{-1}.

(d) Preparation of N-[4-{2-Methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethyl aminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]}-2-hydroxyphenyl] N'- (pyrid-4-yl)urea

A mixture of 2-methoxycarbonyl-1-(benzo[1,3]dioxol-5-yl)ethylaminocarbonyl (S)-(2-methylpropyl)methylaminocarbonylmethyl]-3-t-butyldimethylsilyloxy-4-isocyanatobenzene (165mg), dichloromethane(1mL) and 4-aminopyridine(100mg) was stirred at ambient temperature for 18h. Ethyl acetate was added and the mixture was washed successively with water and brine, dried and evaporated to dryness. A mixture of the residue, potassium fluoride(32mg), N,N-dimethylformamide(1mL) and 48% hydrogen bromide solution(1.5μL) was stirred at room temperature for 18h. The mixture was treated with water and ethyl acetate and stirred while adding sodium hydrogen carbonate until the mixture was basic. The ethyl acetate phase was washed with brine, dried and evaporated to dryness to give product (150mg),[m/e606,MH+].

Preparing the amine and the acid components under standard peptide coupling conditions which constitutes the penultimate stage of the process

Method 1

Preparation of t-Butyl 3-(phenyl)-4-hydroxybutanoate

Borane-THF-complex 1M in THF (12.3mL) was added to a solution of 3-t-butoxycarbonyl- 2-phenylpropanoic acid(2.8g) in dry THF(40mL) at 0°C under argon over 10 min. The mixture was allowed to warm to ambient temperature and stirred for 4 hours. The reaction was then quenched with methanol (10mL) and stirred for a further 30 min. The volatile solvents were removed by evaporation under reduced pressure and the residue dissolved in dichloromethane (100mL), washed with saturated brine (2x20 mL), dried ($MgSO_4$), evaporated under reduced pressure to give product (1.7g) which was used without purification in the next step.

1H NMR (DMSO-d6, 300 MHz, ppm): 1.2(9H,s), 2.3-2.4(1H,dd), 2.7-2.8(1H,dd), 3.0-3.1(1H,m), 3.4-3.6(2H,d), 7.1-7.3(5H,m): m/Z 237 (M+H)

1a) Preparation of 3-t-butoxycarbonyl-2-phenylpropanoic acid

Phenylacetic acid (6.81g) was added to a stirred suspension of sodium hydride (2.20g) in THF(200mL) and diisopropylamine (7.0mL) under argon. The mixture was heated briefly to reflux, stirred for 30min at ambient temperature then cooled to 0°C. A solution of n-butyl lithium (1.6m in hexane) (32.0mL) was added slowly while maintaining the temperature of the mixture below 5°C. The mixture was warmed to 30°C till a solution was formed, then cooled to 10°C and t-butyl bromoacetate (8.10mL) was added and the resultant solution stirred overnight at ambient temperature. The solution was then added to ice water (200mL) and extracted with diethylether (100mL). The organic layer was washed with water (50mL) and the combined aqueous extracts acidified with 2N HCl and extracted with ethyl acetate(3x100mL). The combined ethyl acetate extracts were washed with 50% aqueous brine, dried ($MgSO_4$), evaporated under reduced pressure and purified using a Biotage system, eluting with 15 % ethyl acetate/ hexane to give product (2.82g).

1H NMR (DMSO-d6, 300 MHz, ppm): 1.3(9H,s), 2.4-2.5(1H,dd), 2.8-2.9(1H,dd), 3.8(1H,m), 7.2-7.4(5H,m): m/Z 249 (M-H) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 16.29 min

Method 2

Preparation of t-Butyl 3-carboxy-4-(4-isopropoxyphenyl)butanoate

t-Butyl 3-methoxycarbonyl-4-(4-isopropoxyphenyl)butanoate(2.3g) was dissolved in THF(54mL)/MeOH(18mL) and treated with a 1N solution of lithium hydroxide in water(14.6mL). After stirring at ambient temperature for 4 hours the organic solvents were removed by evaporation under reduced pressure and the residue acidified using 3N citric acid and then extracted with ethyl acetate(3x30mL). The combined ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give product.

1H NMR (DMSO-d6, 300 MHz, ppm): 1.2(6H,d), 1.3(9H,s), 2.1-2.4(2H,m), 2.6(1H,m), 2.8(2H,m), 4.5(1H,m), 6.8(2H,d), 7.0(2H,d) : m/Z 321(M-H), 323(M+H).

2a) Preparation of t-Butyl 3-methoxycarbonyl-4-(4-isopropoxyphenyl) butanoate

4-isopropoxybenzaldehyde was reacted with t-butyl-3-carboxymethyl-3-phophonodimethyl propionate in the manner described by W.M.Owton, P.T.Gallagher and A.Juan-Montesinos in Synthetic Communications, 23(15), 2119-2125 1993) to give the intermediate t-butyl 3-carboxymethyl-4-(4-isopropoxyphenyl)but-3-enoate. This was immediately taken up in methanol containing 5% palladium on carbon and exposed to an atmosphere of hydrogen to give product which was purified using the Biotage system and eluting with toluene.

1H NMR (DMSO-d6, 300 MHz, ppm): 1.2(6H,d), 1.3(9H,s), 2.2-2.5(2H,m), 2.6-2.8(2H,m), 2.9(1H,m), 3.6(3H,s), 4.5(1H,m), 6.8(2H,d), 7.0(2H,d) : m/Z 337(M+H)

t-Butyl-3-carboxy-4-(4-isopropoxyphenyl)butanoate was reacted in place of 3-t-butoxycarbonyl-2-phenylpropanoic acid in the reaction 1b above.

Method 3

Preparation of t-Butyl (3S)-3-allyl-4-hydroxybutanoate

3-[2-(2S)-t-butoxycarbonylmethylpent-4-enoyl]-(4S)-4-isopropyl-oxazolidinone was reduced by the method described by T.D.Penning, S.W.Djuric, R.A.Haack, V.J.Kalish, J.M.Miyashiro, B.W.Rowell and S.S.Yu in Syn.Comm 1990, 20(2), 307-312 to give the product.

1H NMR ($CDCl_3$, 300 MHz, ppm): 1.3(9H,s), 1.9(1H,t) 2.0-2.2(3H,m), 2.3(2H,d), 3.5-3.7(2H,m), 5.0-5.1(2H,m), 5.7-5.9(1H,m) : $[\alpha]_D$ = -9.8(1,EtOAc)

3a) Preparation of 3-[4-Pentenoyl]-(4R)-4-isopropyl-oxazolidinone

This was prepared by the method described by D.A.Evans, J.Bartroli and T.L.Shih in J.A.C.S 1981, 103, 2127 using 4-pentenoyl chloride.

1H NMR ($CDCl_3$, 300 MHz, ppm): 0.9(6H,m), 2.3-2.5(3H,m), 2.9-3.2(2H,m), 4.2-4.4(2H.m), 4.5(1H,m), 5.0-5.2(2H,m), 5.8-5.9(1H,m) : m/Z 212 (M+H)

3b) Preparation of 3-[2-(2S)-t-Butoxycarbonylmethylpent-4-enoyl]-(4S)-4-isopropyl-oxazolidinone

3-[4-pentenoyl]-(4R)-4-isopropyl-oxazolidinone was alkylated by the method described by D.A.Evans, M.D.Ennis and D.J.Mathre in J.A.C.S 1982, 104, 1737 using t-butyl bromoacetate to give the product.

1H NMR ($CDCl_3$, 300 MHz, ppm): 0.9(6H,m), 1.4(9H,s), 2.1-2.2(1H,m), 2.3-2.4(3H,m), 2.7-2.8(1H,dd), 4.1-4.3(3H.m), 4.4(1H,m), 5.0-5.1(2H,m), 5.7-5.8(1H,m) : m/Z 326 (M+H)

Method 4a - Preparation of t-Butyl 3-(phenyl)-4-(3-nitrophenoxy)butanoate

Diethylazodicarboxylate(0.66mL) was added to a solution of 3-(phenyl)-4-hydroxybutyric acid t-butyl ester(1.00g), 3-nitrophenol(0.58g) and triphenylphosphine(1.10g) in THF (10mL) at 0°C under argon over a period of 30 min. The resultant solution was allowed to warm to ambient temperature, stirred overnight and then evaporated under reduced pressure. The residual oil was taken up in toluene, filtered and purified using a Biotage system, eluting with toluene to give the product (1.14g).

1H NMR (DMSO-d6, 300 MHz, ppm): 1.2(9H,s), 2.5-2.7(1H,dd), 2.8-2.9(1H,dd), 3.4-3.5(1H,m), 4.2(2H,d), 7.1-7.4(5H,m), 7.5-7.6(1H,t), 7.7(1H,s), 7.8(1H,d) : m/Z 358 (M+H)

Method 4b - Preparation of t-Butyl 4-(2-cyano-5-nitrophenoxy)butyrate

A mixture of 2-cyano-4-nitrophenol {J.Amer.Chem.Soc.,74 (1952) 2226} (0.2g. 1.23mmole) , methyl 4-bromobutyrate (0.25g. 1.35mmole) and potassium carbonate (0.19g.1.35mmole) in DMF (10mL.) was heated and stirred at 80°C for 8 hours. After cooling, the inorganics were filtered off, and the filtrate evaporated to dryness. The residue was dissolved in dichloromethane and washed twice with water. After drying ($MgSO_4$) the solvent was evaporated off to yield an oil. The oil was purified by chromatography (Varian Megabondelut silica column) using a gradient of 100% dichloromethane to 20% ethyl acetate/ dichloromethane to give the product as an oil (0.1g. 29%) ms 265(M+)

Method 5a - Preparation of t-Butyl 3-(phenyl)-4-(3-aminophenoxy)butanoate

At ambient temperature a rapidly stirred solution of 3-(phenyl)-4-(3-nitrophenoxy)butyric acid t-butyl ester(400mg) in ethanol (20mL) containing 10% palladium on carbon (40mg) was exposed to an atmosphere of hydrogen. When uptake of hydrogen had

ceased the solution was filtered and the filter cake washed with ethanol. The combined filtrates were evaporated to dryness under reduced pressure to give the product (317mg) as an oil.

1H NMR (DMSO-d6, 300 MHz, ppm): 1.2(9H,s), 2.5-2.6(1H,dd), 2.7-2.8(1H,dd), 3.4(1H,m), 3.9(2H,d), 5.0(2H,s), 6.0-6.2(3H,m), 6.8-6.9(1H,t), 7.2-7.4(5H,m) : m/Z 328(M+H) HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt. 14.57 min.

Method 5b - Preparation of t-Butyl (3S)-3-allyl,4-(3-aminophenoxy)butyrate

Tin (II) chloride dihydrate(1.5g) was added to a solution of t-butyl (3S)-3-allyl,4-(3-nitrophenoxy)butyrate (425mg) in ethanol (4mL) and heated to 60°C for 40 min. After cooling to ambient temperature, water (20mL) was added, the mixture was basifed with 2N sodium hydroxide and then extracted with ethyl acetate (3x30mL). The combined ethyl acetate extracts were washed with brine(2x10mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the product (380mg) as a brown oil which was used without further purification in the next step.

1H NMR ($CDCl_3$, 300 MHz, ppm): 1.4(9H,s), 2.1-2.5(5H,m), 3.5-3.7(2H,s), 3.8(2H,s), 5.0-5.1(2H,m), 5.7-5.9(1H,m), 6.3(3H,m), 7.0(1H,t) : m/Z 292 (M+H)

Method 5c - Preparation of t-Butyl 4-(2-cyano-5-aminophenoxy)butyrate

t-Butyl 4-(2-cyano-5-nitrophenoxy)butyrate(0.1g. 0.38mmole) was dissolved in a mixture of ethanol(6mL.) and water(2mL.). Iron powder (127mg.2.88mmole) and ammonium chloride (15mg.0.7 equiv.) were added and the mixture was refluxed with stirring for 4 hours. After cooling, the inorganics were filtered off and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane and washed twice with water. After drying ($MgSO_4$) the solvent was evaporated to yield the product as a solid (80%) ms233(M-).

Method 6a - Preparation of (±) Methyl 4-bromo-3-methylbutyrate

Methyl 3-methylglutarate(37g; 231mmol) was added to 1M NaOH (231mL; 231mmol) causing the solution to warm slightly. This solution was then added to a solution of silver nitrate (39.2g; 231mmol) in water (184mL) at ≈60°C. A fine white precipitate formed immediately. The mixture was cooled and stirred in an ice bath for 1h before being filtered, washed with water, acetone and ether and partially dried on the filter. The solid was

then dried over night at 80°C in a vacuum oven to give the silver salt of the methyl 3-methylglutarate(49g, 79%) as a pale brown solid. The silver salt of the methyl 3-methylglutarate (49g; 184mmol) was suspended in carbon tetrachloride (245mL) and bromine (9.5mL) slowly added. The reaction mixture warmed to ≈30°C during this process and effervescence was seen. The reaction mixture was maintained at this temperature by the rate of addition of bromine. After the final addition of bromine the viscous mixture was stirred for 0.5h before being heated at reflux for 1h. After cooling, the pale yellow precipitate was removed by filtration and the filtrate washed with 1M aqueous sodium thiosulphate , brine, dried (phase separation paper) and concentrated under reduced pressure. This gave a pale yellow oil which contained 15% of methyl 3-methylglutarate as an impurity by ^{1}H NMR. This was removed by taking the oil up in DCM and washing with 1M NaOH. Drying and concentration as above gave the product (25g, 70%) as a pale yellow oil.

^{1}H NMR (300MHz; $CDCl_3$) 1.10 (3H, d), 2.30 (2H, m), 2.55 (1H, dd), 3.40 (1H, dd), 3.45 (1H, dd), 3.70 (3H, s).

i) **Preparation of methyl 3-methylglutarate**

3-Methylglutaric anhydride (50g; 390mmol) and dry methanol (15.8mL; 390mmol) were heated to reflux (≈100°C). After 1h the mixture stopped refluxing but was maintain at 100°C overnight. After cooling, the mixture was distilled (≈95°C at 0.2mmHg) to give the product (37g, 59%) as a colourless oil.

MS (ES-) 159.0 $(M-H)^-$. (ES+) 161.0 $(M+H)^+$

^{1}H NMR (300MHz; $CDCl_3$) 1.10 (3H, d), 2.30 (2H, m), 2.45 (3H, m), 3.70 (3H, s).

Method 6b - Preparation of (S) ethyl 4-bromo-3-methybutyrate

A solution of (S) β-methyl-γ-butyrolactone (5.48g, 54.7mmol. [Aldrich]) in ethanol (120mL) was cooled in an ice/water bath and hydrogen bromide gas passed through the solution for 4.5h at a rate such that the reaction temperature did not exceed 10°C. After this time the pale yellow reaction mixture was stored at 4°C for 3hr. and at -20°C for 14 hr. The reaction mixture was poured onto ice (200mL) and the solution neutralised by the addition of solid sodium carbonate. The aqueous solution was extracted with ethyl acetate (x2) and the

combined extracts dried ($MgSO_4$) and concentrated under reduced pressure to give the product as a pale yellow oil.

^1H NMR (300MHz; $CDCl_3$) 1.10 (3H, d), 1.25 (3H, t), 2.30 (2H, m), 2.55 (1H, dd), 3.45 (2H, m), 4.15 (2H, q).

Method 7 - Preparation of Methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-pent-4-enoate

A solution of the methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate(380mg) in ethanol(2mL) was treated with tosyl hydrazine and heated to reflux for 15 min. then evaporated to dryness under reduced pressure to give methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5- tosylhydrazine-pentanoate.

m/Z 540 (M+H) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 21.10 min.

This was then dissolved in toluene(20mL) filtered through Celite treated with lithium hydride(150mg) under argon and then refluxed for 8 hours. After cooling, the solution was filtered through Celite into 1N H_2SO_4(20mL). The organic phase was separated, washed with water(10mL) and saturated brine(10mL), dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was purified using a 10g "Bond Elute", eluting with toluene to give the product (88mg).

1H NMR (CDCl3, 300 MHz, ppm) : 2.6-2.9(2H,m), 3.6(0.75H,s), 3.7(2.25H,s), 4.0(0.75H,m), 4.2(0.25H,m), 5.9(2.25H,m), 6.4(1.5H,d), 6.6(0.25H,d), 6.7-6.8(3H,m), 7.4-7.7(2H,m), 8.1-8.3(2H,m): m/Z 356 (M+H) .

The (benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-pent-4-enoate was reduced using the procedure described in 5b to give, after further processing the final product of example 134.

7i) Preparation of 1-(3-Nitrophenyl)-3-(3,4-[methylenedioxy]phenyl)prop-2-ene-1-one

This was prepared using the procedure described in Vogel pg 1034 starting from piperonal and 3-nitroacetophenone.

1H NMR (DMSO-d6, 300 MHz, ppm) : 6.1(2H,s), 7.0(1H,d), 7.4(1H,d), 7.7-7.9(4H,m), 8.4(1H,d), 8.6(1H,d), 8.8(1H,s): m/Z 298 (M+H).

7ii) Preparation of Methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate

1-(3-nitrophenyl)-3-(benzo[1,3]dioxyol-5-yl)prop-2-ene-1-one was treated with dimethyl malonate in the manner described by Davey and Gwilth in J.C.S. 1957 p.1015 to give the product.

1H NMR (DMSO-d6, 300 MHz, ppm) : 3.4-3.5(4H,m), 3.6-3.8(4H,m), 3.8-3.9(1H,dt), 3.9-4.1(1H,m), 5.9(2H,d), 6.7(2H,m), 6.9(1H,s), 7.8(1H,t), 8.3(1H,d), 8.4(1H,d), 8.6(1H,s) : m/Z 430 (M+H) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 18.69 min.

7iii) Preparation of 2-Carboxy-3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoic acid

The methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate was hydrolysed using the procedure described method to give the product. 1H NMR (DMSO-d6, 300 MHz, ppm) : 3.4-3.5(1H,m), 3.6-3.9(3H,m), 5.9(2H,d), 6.7(2H,s), 6.9(1H,s), 7.8(1H,t), 8.3(1H,d), 8.4(1H,d), 8.6(1H,s) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 13.00 min.

7iv) Preparation of 3-(Benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoic acid

2-Carboxy-3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoic acid was decarboxylated using the procedure described by Toussaint, Capdeville and Maumy in Synthesis 1986 pp1029-1030 to give the product.

1H NMR (DMSO-d6, 300 MHz, ppm) : 2.4-2.7(2H,m), 3.4-3.7(3H,m), 5.9(2H,d), 6.7(2H,q), 6.9(1H,s), 7.8(1H,t), 8.3(1H,d), 8.4(1H,d), 8.6(1H,s), 12.1(1H,b) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 15.22 min

7v) Preparation of Methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate

The 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoic acid was re-esterified to give the product.

1H NMR (DMSO-d6, 300 MHz, ppm) : 2.5-2.8(2H,dq), 3.4-3.7(6H,m), 5.9(2H,d), 6.7(2H,q), 6.9(1H,s), 7.8(1H,t), 8.3(1H,d), 8.4(1H,d), 8.6(1H,s),: m/Z 371 (M+H) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 18.63 min

The methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate was reduced using the procedure described in 5a and further processed to give example 132 as the final product.

The methyl 3-(benzo[1,3]dioxyol-5-yl)-5-nitrophenyl-5-oxo-pentanoate was reduced using the procedure described in 5b and further processed to give example 135 as the final product.

This demonstrates that the use of a different reducing agent gives a different amine.

Method 7a - Preparation of methyl 2-methoxycarbonyl -3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentenoate

At ambient temperature a rapidly stirred solution of methyl 2- methoxycarbonyl-3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentynoate(205mg) in ethanol(15mL)containing Lindlar catalyst (60mg) was exposed to an atmosphere of hydrogen. When uptake of hydrogen had ceased, the solution was filtered and the filter cake washed with ethanol. The combined filtrates were evaporated to dryness under reduced pressure and purified using a 10g Bond Elute, eluting with 5% ethyl acetate/toluene to give the product (110mg).

1H NMR (CDCl3, 300 MHz, ppm) : 3.5-3.9(7H,m), 4.2(0.2H,m), 4.5(0.8H,m), 5.9(2H,s), 6.1(0.8H,t), 6.5(0.4H,m), 6.6(0.8H, d), 6.7-6.8(3H,m), (7.4-7.6(2H,m), 8.1-8.2(2H,m) : m/Z 431 ($M+NH_4$) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 20.06 min

The methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentenoate was reduced using the procedure described in 5b, coupled using the procedure described in Aii, saponified using procedure Ib and decarboxylated using the procedure described in method IV to finally give the final product of example 138.

The methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentynoate was reduced using the procedure described in 5b, coupled using the procedure

described in Ai, saponified using procedure Ib and decarboxylated using the procedure described in final Stage IV to give example 136.

The methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentynoate was reduced using the procedure described in 5a, coupled using the procedure described in Ai, saponified using procedure Ib and decarboxylated using the procedure described in final Stage IV to give example 137.

7a i) Preparation of Methyl 2-methoxycarbonyl-3-(benzo[1,3]dioxyol-5-yl)-2-propenoate

Methyl 2-methoxycarbonyl-3-(benzo[1,3]dioxyol-5-yl)-2-propenoate was prepared using the procedure described by Lehnert in Tetrahedron Letters 54 pp 4723-4724 1970, starting from piperonal and dimethyl malonate.

1H NMR (CDCl3, 300 MHz, ppm) : 3.8(3H,s), 3.9(3H,s), 6.0(2H,s), 6.8(1H, d), 6.9(1H,s), 7.0(1H,d), 7.6(1H,s), m/Z 265 (M+H)

7a ii) Preparation of Methyl 2-methoxycarbonyl-3-(benzo[1,3]dioxyol-5-yl)-5-trimethylsilyl-4-pentynoate

A solution of methyl 2-methoxycarbonyl-3-(benzo[1,3]dioxyol-5-yl)-2-propenoate(2.64g) in THF(5mL) was added dropwise to a stirred solution of trimethylsilylethynyl magnesium bromide in THF (32mL) at 0°C under argon over 1 hour. The reaction was stirred for a further 30 min. after the addition was complete. It was then poured into ice cold 2N HCl(25mL), the organic phase was separated and the aqueous phase extracted with ether(2x20mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution(10mL), water(10mL), saturated brine(10mL), dried ($MgSO_4$), evaporated to dryness and purified using the Biotage system eluting with 5% ethyl acetate/hexane to give the product(1.4g)

1H NMR (CDCl3, 300 MHz, ppm) : 0.5(9H,s), 3.6(3H,s), 3.7(1H,d), 3.8(3H,s), 4.4(1H,d), 5.9(2H,s), 6.7(1H, d), 6.8(1H,d), 6.9(1H,s) : m/Z 363 (M+H) .

7a iii) Preparation of Methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-4-pentynoate

A solution of methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-5-trimethylsilyl-4-pentynoate(3.62g) in THF (30mL) was added to 1M tetrabutylammoniumfluoride in THF(20mL) at 0°C. After stirring for 1hour at 0°C, saturated ammonium chloride (30mL)was added and the mixture extracted with ether (4x30mL), dried($MgSO_4$), evaporated to dryness and puified using the Biotage system eluting with 10% ethyl acetate/ hexane to give product (2.12g).

1H NMR (CDCl3, 300 MHz, ppm) : 2.3 (1H,s), 3.6(3H,s), 3.7(1H,d), 3.8(3H,s), 4.4(1H,d), 5.9(2H,s), 6.7(1H, d), 6.8(1H,d), 6.9(1H,s) : m/Z 291 (M+H)

7a iv) Preparation of Methyl 2- methoxycarbonyl -3-(benzo[1,3]dioxyol-5-yl)-5-(3-nitrophenyl)-4-pentynoate

A solution of methyl 2-carbomethoxy-3-(benzo[1,3]dioxyol-5-yl)-4-pentynoate(2.1g) and 1-iodo-3-nitrobenzene(1.8g) in triethylamine(20mL) was degassed by bubbling through argon for 30 min. before adding bis triphenylphosphinepalladium chloride(100mg) followed by copper(I) iodide(26mg). The mixture was stirred at ambient temperature for 1 hour. The mixture then was evaporated to dryness and the residue dissolved in ether(50mL), washed with water(2x20mL), dried ($MgSO_4$) and purified using the Biotage system eluting with 15% ethyl acetate/hexane to give the product (2.5g).

1H NMR (CDCl3, 300 MHz, ppm) : 2.3 (1H,s), 3.6(3H,s), 3.7(1H,d), 3.8(3H,s), 4.6(1H,d), 5.9(2H,s), 6.8(1H, d), 6.9(1H,d), 7.0(1H,s), 7.5(1H,t), 7.7(1H,d), 8.1(1H,d), 8.2(1H,s) : m/Z 412 (M+H) : HPLC Dynmax 60A C18 column : Acetonitrile/water/0.1%TFA 20-80% over 20 min Rt 20.52 min.

Method 8 - Preparation of ester prodrugs

This is described in example 8 above.

Method 9 - Preparation of Ethyl 4-(3-nitrophenoxy)-3-hydroxybutyrate

A mixture of ethyl 4-(3-nitrophenoxy)-3-oxobutyrate(3.8g), sodium cyanoborohydride(1g), tetrahydrofuran(30mL) and ethanol(30mL) was stirred at room temperature for 120h, treated with sodium cyanoborohydride(0.25g) and stirred for a further

24h. The mixture was acidified with glacial acetic acid and evaporated to near dryness under reduced pressure. The residue was partitioned between water and ether and the ether phase was separated, washed with brine, dried and evaporated to dryness to give the product (3.8g)[m/e270 MH+] as a pale yellow gum. This is used in the preparation of example 22

9i) Preparation of Ethyl 4-(3-nitrophenoxy)-3-oxobutyrate

1,1-Carbonyldiimidazole(5.1g) was added to a stirred, suspension of 3-nitrophenoxyacetic acid(3.94g) in dichloromethane(20mL) at 0°C and the mixture was stirred and allowed to warm to room temperature over 3h. The mixture was added to a stirred mixture of Meldrum's acid(4.54g), dichloromethane(20mL) and pyridine(5.1mL). 4-Dimethylaminopyridine(0.06g) was added and the mixture stirred at ambient temperature for 120h. The mixture was washed successively with water, 2NHCL and brine and then dried and evaporated to dryness under reduced pressure. The residue was treated with ethanol(50mL) and the mixture heated at reflux for 4h, then cooled and evaporated to dryness under reduced pressure. The residue was triturated with 1:1 ether:hexane mixture and the insoluble white solid collected to give the product(4.55g). [m/e268 MH+].

Method 10 - Preparation of 2-(N-Methylanilino)-6-carboxymethylbenzoxazole

2-(N-methylanilino)-6-methoxycarbonylmethylbenzoxazole was hydrolysed by the process described in final stage I to give the product [m/e283,MH+].

10i) Preparation of 2-(N-Methylanilino)-6-methoxycarbonyl methyl benzoxazole

A 1M solution of lithium diisopropylamide in hexane(0.6mL) was added to a stirred mixture of 2-anilino-6-methoxycarbonylmethylbenzoxazole(153mg), iodomethane(154mg) and tetrahydrofuran(3mL) at -70°C. The mixture was allowed to warm to room temperature and stirred under an atmosphere of argon for 18h. The mixture was acidified with acetic acid, partitioned between water and ether. The resultant organic phase was washed with brine, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (54mg) [m/e297 MH+] as a gum.

Method 11 - Preparation of 2-Anilino-4-methoxy-6-methoxycarbonylmethylbenzoxazole

A mixture of methyl 3-benzyloxy-5-methoxy-4-nitrophenylacetate (1.7g), 10% palladium on carbon catalyst(0.2g), tetrahydrofuran(15mL) and ethanol(15mL) was stirred under an atmosphere of hydrogen for 18h. The mixture was filtered and the filtrate treated with phenylisothiocyanate(0.72g) followed by yellow mercuric oxide(1.55g). The mixture was stirred at reflux for 2h, treated with a further portion of mercuric oxide (1.55g) and refluxed for a further 1h. The mixture was then filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product. [m/e313,MH+].

2-Anilino-4-methoxy-6-methoxycarbonylmethylbenzoxazole was then hydrolysed by the process described in final stage I to give 2-anilino-4-methoxy-6-carboxylmethyl benzoxazole which was then used in preparation of example 32

11i) Preparation of 3,5-Difluoro-2-nitrophenol

A solution of 2,4,6-trifluoronitrobenzene (10g) in dimethyl sulphoxide(50 mL) was treated with 10N sodium hydroxide(12 mL) and the mixture was stirred at room temperature for 18h. The mixture was diluted with water and washed with ether. The aqueous phase was then acidified and extracted with ether. The extract was washed with brine, dried and evaporated to dryness and the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(8.3g) [m/e174,MH-].

11ii) - Preparation of 3,5-Difluoro-2-nitro-anisole

A mixture of 3,5 difluoro-2-nitrophenol(8.3g), N,N-dimethylformamide(30mL), potassium carbonate(10g) and iodomethane(5mL) was stirred vigorously at room temperature for 18h. The mixture was diluted with water and extracted with ether. The extract was washed with brine, dried and evaporated to dryness to give the product(8.7g) as a yellow solid.

11iii) - Preparation of Di-t-butyl 3-fluoro-5-methoxy-4-nitrophenylmalonate

Di-t-butyl malonate(18g) was added dropwise to a stirred suspension of sodium hydride[60% dispersion in mineral oil](3.3g) in N-methyl pyrrolidinone(100mL) under an atmosphere of argon and the mixture was stirred until effervescence ceased. 3,5 Difluoro-2-

nitro-anisole(6.4g) was added and the mixture was stirred at 80°C for 2h. The mixture was cooled to room temperature then partitioned between water and ether and then the ether extract was dried and evaporated to dryness. The residue was subjected to flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(5.5g)

11iv) - Preparation of Methyl 3-benzyloxy-5-methoxy-4-nitrophenylacetate

A suspension of di-t-butyl 3-fluoro-5-methoxy-4-nitrophenylmalonate(5.5g) in 1:1 5N hydrochloric acid :acetic acid(15mL) stirred at reflux for 4h and then evaporated to dryness. The residue was partitioned between 2N sodium hydroxide and ether. The aqueous phase was acidified and extracted with ether. The extract was washed with brine, dried and evaporated to dryness. A solution of the residue in benzyl alcohol(15mL) was stirred under argon and treated with sodium hydride, [60%dispersion in mineral oil](1.2g). The resultant mixture was stirred at 65°C for 18h then cooled and partitioned between water andethyl acetate. The aqueous phase was acidfied and extracted with ethyl acetate and the extract dried and evaporated to dryness. A solution of the residue in methanol(50mL) was treated with concentrated sulphuric acid(1mL) and the solution refluxed for 2h. The cooled solution was diluted with water and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, brine, dried and evaporated to dryness. The residue then was subjected to flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(2.85g). [m/e332,MH+]

Method 12a - Preparation of 2-Phenylaminobenzoxazole-6-acetic acid

This is described in example 1 above. 12 step 3 is step c) of example 1.

An alternative method for the preparation of methyl 2-phenylaminobenzoxazole-6-acetate which avoided the use of mercuric oxide and could be operated on a 2 molar scale is described below.

12a i) Alternative preparation for Methyl 2-phenylaminobenzoxazole-6-acetate

Under an argon atmosphere, methyl 3-hydroxy-4-nitrophenylacetate (344g, 1.63 mol) was added to a stirred suspension of 10% palladium/carbon (50g) in ethanol (6L). The argon was replaced by hydrogen, the mixture stirred for 4hr. and the catalyst then removed by filtration. The filtrate was evaporated and the residue taken up in ethyl acetate(10 L)

Phenylisocyanate (195g, 178ml,1.63 mol) was added to this stirred solution, which contained methyl 4-amino-3-hydroxyphenyl acetate, maintained at ambient temperature. After 5hr the solvent was removed to give methyl 3-hydroxy-4-phenylureidophenylacetate as a pink solid (480g, 98%) which was sufficiently pure to be used directly in the next stage. Diethyl azodicarboxylate (273ml, 302g, 1.73mols) was added dropwise over 1 hour to a stirred solution of the methyl 3-hydroxy-4-phenylureidophenylacetate (520g, 1.73mols) and triphenylphosphine (908g, 3.46mols) in THF (5.2 L) maintained at -10°C. The reaction mixture was then allowed to warm to ambient temperature (25°C) and stirred at this temperature for 48 hours. The THF was removed in vacuo. The residue was dispersed in diethyl ether (2.0 litres) and the mixture filtered. The filter cake was washed with diethyl ether (300ml) and the combined filtrates were evaporated. The residue was taken up in dichloromethane(3.0 litres) and passed through a pad of silica (1 kg). The silica pad was washed with dichloromethane (5.0 litres). The solvent was evaporated and the residue was purified by chromatography on silica get using 25% (v/v) ethyl acetate/iso-hexane as eluant. Yield 284g (55%). The material was identical to that produced in example 1e.

Method 12b - Preparation of Methyl 3-hydroxy-5-fluoro-4-nitrophenylacetate

A suspension of di-t-butyl 3-fluoro-5-benzyloxy-4-nitrophenylmalonate(0.22g) in 1:1 5N HCl:HOAC(10mL) stirred at reflux for 1h and then evaporated to dryness. A solution of the residue in MeOH(20mL) was treated with conc H_2SO_4(0.5mL) and the solution refluxed for 1h. The cooled solution was diluted with water and extracted with ether and the ether extract washed with water, brine, dried and evaporated to dryness. The residue was subjected to flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.11g). [m/e228,MH-]. This was then used in Method 11 v to give ultimately the products of examples 36 and 37.

12bi) Preparation of 2-Benzyloxy-4,6-difluoronitrobenzene

A mixture of 3,5 difluoro-2-nitrophenol(5.3g), N,N-dimethylformamide(30mL), potassium carbonate(6g) and benzyl bromide(6g) was stirred at 60°C for 1h. The mixture was diluted with water, extracted with ether and the extract was washed with brine, dried and evaporated to dryness. The residue was stirred with hexane and the insoluble solid was collected to give the product (7.1g) as a light yellow solid.

12bii) Preparation of Di-t-butyl 3-fluoro-5-benzyloxy-4-nitrophenylmalonate

Di-t-butyl malonate(1.72g) was added dropwise to a stirred suspension of sodium hydride[60% dispersion in mineral oil](0.3g) in N-methyl pyrrolidinone(10mL) under an atmosphere of argon and the mixture was stirred until effervescence ceased. 2-benzyloxy-4,6-difluoronitrobenzene(0.85g) was added and the mixture was stirred at 80°C for 2h. The mixture was cooled to room temperature then partitioned between water and ether. The ether extract was dried and evaporated to dryness. The residue was subjected to flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(0.4g) [m/e460,MH-].

Method 12c - Preparation of methyl-2-(3-benzyloxy-4-nitrophenyl)propionate and dimethyl-2-(3-benzyloxy-4-nitrophenyl)-2-methylmalonate

a) Preparation of dimethyl-2-(3-benzyloxy-4-nitrophenyl)-2-methylmalonate

A mixture of dimethyl-(3-benzyloxy-4-nitrophenyl)malonate(2.3g), N-methylpyrrolidinone(15mL) and a 60% dispersion of sodium hydride in mineral oil(0.31g) was stirred under an argon atmosphere at 0°C for 0.5h. The mixture was treated with iodomethane(0.8mL) and stirred at ambient temperature for 4h then treated with water (50mL). The precipitate was collected and washed with water and hexane to give dimethyl-2-(3-benzyloxy-4-nitrophenyl)-2-methylmalonate(2.19g). [m/e374(MH+)].

b) Preparation of 2-(3-benzyloxy-4-nitrophenyl)propionic acid

A mixture of dimethyl-2-[(3-benzyloxy-4-nitrophenyl)]-2-methylmalonate(2.16g), methanol(10mL), tetrahydrofuran(10mL) and 2N sodium hydroxide(10mL) was stirred at ambient temperature for 3h. The solution was acidified with 2N hydrochloric acid and the mixture was extracted with ether and the extract washed with brine, dried and evaporated to dryness to give 2-(3-benzyloxy-4-nitrophenyl)propionic acid as a tan solid(1.89g). [m/e319(MNH4+)].

c) Preparation of methyl- 2-(3-benzyloxy-4-nitrophenyl)propionate

A mixture of 2-(3-benzyloxy-4-nitrophenyl)propionic acid(1.89g), methanol(30mL) and concentrated sulphuric acid(1mL) was heated at reflux for 3h, cooled to ambient temperature and the mixture was extracted with ether. The extract washed with brine, dried and evaporated to dryness to give methyl- 2-(3-benzyloxy-4-nitrophenyl)propionate(1.8g). [m/e316(MH+)].

d) Preparation of dimethyl-2-(3-benzyloxy-4-nitrophenyl)-2-methylmalonate

A mixture of methyl- 2-(3-benzyloxy-4-nitrophenyl)propionate(0.8g), N-methylpyrrolidinone(5mL) and a 60% dispersion of sodium hydride in mineral oil(0.19g) was stirred under an argon atmosphere at 0°C for 0.5h. The mixture was treated with iodomethane(0.45mL) and stirred at ambient temperature for 1h then treated with water (50mL). The precipitate was collected and washed with water and hexane to give the product (2.19g). [m/e330(MH+)].

Method 13 - Preparation of Methyl 4-(N-methylaminophenoxy)butyrate

A solution of methyl 4-(3-t-butoxycarbonyl-[N-methyl]aminophenoxy)butyrate(0.2g) in a mixture of dichloromethane(1mL) and trifluoroacetic acid(1mL) was kept at ambient temperature for 1h and evaporated to dryness. The residue was treated with water and ethyl acetate and the mixture was stirred while making basic with potassium carbonate. The organic phase was separated, dried and evaporated to dryness to give the product (0.14g), [m/e224,MH+].

13i) Preparation of Methyl 4-(3-t-butoxycarbonylaminophenoxy)butyrate

A mixture of methyl 4-(3-aminophenoxy)butyrate(0.42g), tetrahydrofuran(5mL) and di-t-butyl dicarbonate(0.44g) was stirred at 60-70°C for 18h. The mixture was evaporated to dryness and the residue was then purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.6g),[m/e310,MH+].

13ii) Preparation of Methyl 4-(3-t-butoxycarbonyl-[N-methyl]amino phenoxy) butyrate

A mixture of sodium hydride[60% dispersion in mineral oil](0.04g), iodomethane (0.2mL) and N-methyl pyrrolidinone(100mL) was stirred under an atmosphere of argon and treated with methyl 4-(3-t-butoxycarbonylaminophenoxy)butyrate(0.2g). The mixture was stirred at ambient temperature for 0.5h, treated with water and then extracted with ether. The ether extract was washed successively with water and brine, dried and evaporated to dryness to give the product(0.21g), [m/e324,MH+].

Method 14 - Preparation of 2-Anilino 6-[2-(2,2-dimethylaminoethoxycarbonyl)1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl) methylamino carbonylmethyl]benzoxazole

A mixture of 2-(2,2-dimethylaminoethoxycarbonyl)1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylamine(0.1g), 6-carboxymethyl-2-anilinobenzoxazole(0.1g), hydroxybenzotriazole (0.05g), N-methylmorpholine(0.05mL), dimethylformamide(0.5mL) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(0.1g) was stirred for 72hr. The mixture was partitioned between water and ethyl acetate, the organic layer was separated and washed successively with aqueous sodium bicarbonate and brine and then dried and evaporated to dryness. The residue was triturated with ethyl acetate and the insoluble white solid collected to give the product (0.07g)

14i) Preparation of N-t-butoxycarbonyl-[2-(2,2-dimethylaminoethoxyarbonyl) 1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methyl]amine

A mixture of N-t-butoxy carbonyl-[2-carboxy1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methyl]amine(0.21g), dichloromethane(5mL), N,N-dimethylethanolamine(0.2g), dicyclohexylcarbodiimide(0.1g) and 4-dimethlaminopyridine(0.1g) was stirred at room temperature for 72h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was taken up in ether and the solution washed several times with water, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with ethyl acetate followed by mixtures of 99:1 ethyl acetate :triethylamine containing an increasing proportion of methanol to give the product (145mg), [m/e494,MH+].

14ii) Preparation of 2-(2,2-Dimethylaminoethoxycarbonyl)1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylamine

A solution of N-t-butoxycarbonyl-[2-(2,2-dimethylaminoethoxycarbonyl)1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methyl]amine(130mg) in a mixture of dichloromethane(1mL) and trifluoroacetic acid(1mL) was kept at ambient temperature for 1h and evaporated to dryness. The residue was treated with brine (0.5mL), made basic with potassium carbonate and the mixture was extracted several times with

dichloromethane. The extracts were combined, dried and evaporated to dryness to give the product which was used without further purification.

Method 15 - Preparation of 2-[(N-oxidopyrid-3-yl)amino]- 6-[2-Carboxy-1-(benzo[1,3] dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl) methylamino carbonylmethyl] benzoxazole

A mixture of 2-[pyrid-3-ylamino]- 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl) ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzoxazole (0.09g), methanol(2mL) and 3-chloroperbenzoic acid was stirred at ambient temperature for 18h. The insoluble solid was collected and washed with a little methanol and ether to give the product(0.02g).

Method 16 - Preparation of 2-anilino-4-methylthio-6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl-]benzoxazole (example 38)

16i) Preparation of Methyl 3-benzyloxy-5-methylthio-4-nitrophenylacetate

A mixture of di-t-butyl 3-fluoro-5-methoxy-4-nitrophenylmalonate(0.4g), N-methylpyrrolidinone(2mL) and sodium thiomethoxide(0.3)g was stirred at room temperature for 3h. The mixture was diluted with water, acidified with 2N hydrochloric acid and extracted with ether and the extract was dried and evaporated to dryness. The residue was then treated with 1:1 5N hydrochloric acid:acetic acid(5mL) and the mixture was refluxed for1h and then evaporated to dryness. A solution of the residue in methanol(10mL) was treated with concentrated sulphuric acid(0.5mL) and the mixture heated at reflux for 1h. The mixture was then cooled, diluted with water. The resultant mixture was then extracted with ether and the extract was washed with brine, dried and evaporated to dryness . The residue was purified by flash chromatography, eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product. (0.11g), [m/e285,$(M+NH_4)^+$].

16ii) Preparation of 2-Anilino-6-methoxycarbonyl-4-methylthiobenzoxazole

A mixture of methyl 3-benzyloxy-5-methylthio-4-nitrophenylacetate (0.01g), methanol(10mL), water(5mL), ammonium chloride(0.02g) and iron powder(0.01g) was stirred at reflux for 2h. The mixture was treated with ethyl acetate and filtered and the

organic phase was separated, dried and evaporated to dryness. A solution of the residue(75mg) in ethyl acetate was treated with phenylisocyanate and the mixture was stirred at 60°C for 0.5h and evaporated to dryness. A solution of the residue in tetrahydrofuran was treated with tri-n-butylphosphine(0.13g) and 1,1'-(azodicarbonyl)dipiperidine(0.17g) and the mixture was stirred at ambient temperature for 18h. The mixture was treated with 1M aqueous citric acid and ethyl acetate and the organic phase was separated, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.05g). [m/e329,MH+].

16iii)Preparation of 2-anilino-4-methylthio-6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl-]4-methylthio-benzoxazole

2-Anilino-6-methoxycarbonyl-4-methylthiobenzoxazole was hydrolysed by the process described in Method Ia to give 2-anilino-6-carboxy-4-methylthiobenzoxazole [m/e315,MH+] which was used in the Method Ai to give the product.

Method 17 - Preparation of give 2-anilino-4-methylsulphonyl 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl) methylamino carbonylmethyl]benzoxazole (example 39)

A mixture of 2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl-]4-methylthio-benzoxazole(20mg), N,N-dimethylformamide(1mL), water(0.2mL) and oxone{Aldrich}(50mg) was stirred at room temperature for 72h. The mixture was diluted with water and the insoluble white solid collected and dried to give the product(15mg).

Method 18 - Preparation of 2-Anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylsulphonylethyl) methylaminocarbonyl methyl]benzoxazole

i) A mixture of 2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethyl amino carbonyl(S)-(2-methylthioethyl)methylaminocarbonylmethyl]benzoxazole(85mg), N,N-dimethylformamide(2mL), water(0.5mL) and Oxone{Aldrich}(200mg) was stirred at room temperature for 72h. The mixture was diluted with water and ethyl acetate and stirred the insoluble solid collected and dried to give the product (65mg).

ii) The series of processes described in the preparation of example 2 was repeated using methyl 3-(S-methioninylamino)-3-[–benzo[1,3]dioxol-5-yl)phenyl] instead of methyl 3-(S-leucylamino)-3-[–benzo[1,3]dioxol-5-yl)phenyl]propanoate to give 2-anilino 6-[2-Carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylthioethyl) methylaminocarbonyl methyl]benzoxazole.

Method 19 - Preparation of 2-(N-Methylanilino)- 6-[2-methoxycarbonyl-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2- methylpropyl) methylamino carbonylmethyl]4-methoxybenzoxazole

A mixture of 2-anilino 6-[2-methoxycarbonyl-1-(benzo[1,3]dioxoly-5-yl)ethylamino carbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]4-methoxybenzoxazole(75mg), N,N-dimethylformamide(2mL), potassium carbonate(100mg) and iodomethane(0.2mL) was stirred at room temperature for 18h. The mixture was treated with water and ether and stirred and the insoluble white solid collected to give the product (68mg)[m/e 631,MH+].

Method 20

20i) Preparation of 5-Fluoro-3-methoxy-2-nitrophenol

A mixture of 3,5-difluoro-2-nitroanisole(4.36g), dimethylsulphoxide(10mL) and 10N aqueous sodium hydroxide(6.5mL) was stirred at ambient temperature for 18h and then at 60°C for 3h. The mixture was diluted with water and acidified with concentrated hydrochloric acid, extracted with ethyl acetate and the extract was washed with water dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (3.0g),(m/e186,MH-).

20ii) Preparation of 3-Benzyloxy-5-fluoro-2-nitroanisole

A mixture of 5-fluoro-3-methoxy-2-nitrophenol(0.56g), acetonitrile(5mL), potassium carbonate(0.46g) and benzyl bromide(0.56g) was stirred at reflux for 2h. The cooled mixture was treated with water and ethyl acetate and the organic phase was separated, washed with brine, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.82g), (m/e278,MH+).

20iii) Preparation of 3-Benzyloxy-5-methoxy-4-nitrophenol

A mixture of 3-benzyloxy-5-fluoro-2-nitroanisole(0.75g), dimethylsulphoxide(5mL) and 5N aqueous sodium hydroxide(2mL) was stirred at 70°C for 3h. The mixture was diluted with water and acidified with concentrated hydrochloric acid, extracted with ethyl acetate and the extract was washed with water dried and evaporated to dryness to give the product (0.71g), (m/e274,MH-).

20iv) Preparation of Methyl 3-benzyloxy-5-methoxy-4-nitrophenoxyacetate

A mixture of 3-benzyloxy-5-methoxy-4-nitrophenol(3.85g), N,N-dimethyl formamide (20mL), potassium carbonate(2.8g) and methyl bromoacetate(2.42g) was stirred at ambient temperature for 3h. The mixture was treated with water and ethyl acetate and the organic phase was separated, washed with brine, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (4.6g), (m/e348,MH+).

20v) Preparation of 2-Anilino-4-methoxy-6-methoxycarbonylmethoxy benzoxazole

A mixture of methyl 3-benzyloxy-5-methoxy-4-nitrophenoxyacetate(1g), ethanol(30mL) and 10% palladium on carbon catalyst(0.2g) was stirred stirred under an atmosphere of hydrogen for 18h. The mixture was filtered and the filtrate treated with phenylisothiocyanate(0.35mL) followed by yellow mercuric oxide(0.85g). The mixture was stirred at reflux for 4h, then filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.75g),[m/e329MH+].

Method 21 - Preparation of 2-Anilino-5-methoxycarbonylmethylbenzimidazole

2-Anilino-4-methoxy-6-methoxycarbonylmethoxybenzoxazole was hydrolysed by the process described in Method Ia to give 2-anilino-4-methoxy-6-carboxymethoxybenzoxazole [m/e315,MH+] which was used in the process described in methods A(i) and A(ii) to give coupled products.

21i) Preparation of Methyl 4-amino3-nitrophenylacetate

A mixture of 4-amino3-nitrophenylacetic acid(0.7g), methanol(10mL) and concentrated sulphuric acid(0.1mL) was stirred at reflux for 2h. The mixture was cooled, diluted with water and made basic with aqueous sodium hydroxide solution and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to dryness and the residue was triturated with ether and the insoluble yellow solid collected to give the product (0.63g),[m/e211,MH+].

21ii) Preparation of 2-Anilino-5-methoxycarbonylmethylbenzimidazole

A mixture of methyl 4-amino3-nitrophenylacetate(315mg), ethanol(5mL) and 10% palladium on carbon catalyst(50mg) was stirred stirred under an atmosphere of hydrogen for 2h. The mixture was filtered and the filtrate treated with phenylisothiocyanate(202mg). The mixture was stirred at 60°C for 2h, treated with yellow mercuric oxide(430mg) and then stirred at reflux for 18h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and dichloromethane to give the product (240mg),[m/e282,MH+].

2-Anilino-5-methoxycarbonylmethylbenzimidazole was hydrolysed by the process described in Method Ia to give 2-Anilino-5-carboxymethylbenzimidazole[m/e266,MH-] which was then used in the process described in method A(i) to give coupled products.

Method 22 - Preparation of 2-Anilino-6-carboxymethyl-1-methyl-benzimidazole

2-Anilino-6-methoxycarbonylmethyl-1-methylbenzimidazole was hydrolysed by the process described in Method Ia to give 2-anilino-6-carboxymethyl-1-methyl-benzimidazole [m/e280,MH-]. This was then used in the Method A(i) to give coupled products **22i)**

Preparation of Dimethyl (3-fluoro-4-nitrophenyl)malonate

Dimethyl malonate(45.7g) was added dropwise to a stirred mixture of sodium hydride [60%dispersion in oil], (13.8g) and dimethylsulphoxide(300mL) and then the mixture was treated with 2,4-difluoronitrobenzene(25g). The mixture was stirred at 100°C for 1h, then poured onto saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and evaporated to dryness and

the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(5g).

22ii) Preparation of Methyl 3-methylamino-4-nitrophenylacetate

A mixture of dimethyl (3-fluoro-4-nitrophenyl)malonate (0.5g) and a 2M solution of methylamine in tetrahydrofuran(5mL) was stirred at room temperature for 18h and then evaporated to dryness. The residue was treated with a 1:1 mixture of 5N aqueous hydrochloric acid and acetic acid and the mixture was heated at reflux for 4h. The mixture was evaporated to dryness and the residue taken up in methanol(10mL) and the solution treated with concentrated sulphuric acid(0.5mL) and heated at reflux for 2h. Water was added and the mixture was extracted with ethyl acetate and the extract was washed with aqueous sodium hydrogen carbonate solution, dried and evaporated to dryness to give the product as a yellow solid(0.35g), [m/e225,MH+].

22iii) Preparation of 2-Anilino-6-methoxycarbonylmethyl-1-methyl-benzimidazole

A mixture of methyl 3-methylamino-4-nitrophenylacetate(0.34g), 10% palladium on carbon catalyst(0.05g) and ethanol(5mL) was stirred under hydrogen at room temperature and atmospheric pressure for 2h. The mixture was filtered, treated with phenylisothiocyanate (0.2g). The mixture was stirred at 60°C for 2h and then treated with yellow mercuric oxide(0.43g) and stirred at reflux for 4h. The mixture was filtered and the filtrate was evaporated to dryness and the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(0.16g), [m/e296,MH+].

Method 23 - Preparation of 2-Anilino-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl} benzothiazole and 2-anilino 6-[2-carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl)methylaminocarbonylmethyl]benzothiazole

2-anilino-6-methoxycarbonylmethyl benzothiazole was hydrolysed by the process described in Method Ia to give 2-anilino-6-carboxymethylbenzothiazole [m/e283,MH-] which was used in the process described in example A(i) to give, after hydrolysis in each case, 2-anilino-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl}benzothiazole and 2-anilino-6-[2-

carboxy-1-(benzo[1,3]dioxoly-5-yl)ethylaminocarbonyl(S)-(2-methylpropyl) methylaminocarbonylmethyl]benzothiazole (example 33).

23i) Preparation of Methyl 3-(4-methoxybenzylthio)-4-nitrophenylacetate

A mixture of methyl 3-fluoro-4-nitrophenylacetate(1.05g), N-methylpyrrolidinone(10mL) and 4-methoxybenzyl mercaptan was stirred under argon and treated with sodium hydride(0.22g of a 60% dispersion in mineral oil) and the resulting mixture was stirred at ambient temperature for 0.5h. Water was added and the mixture was extracted with ether, and the extract was washed with brine, dried and evaporated to dryness. The residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (1.35g), [m/e365,$(M+NH4)^+$]

23ii) Preparation of Methyl 4-amino-3-(4-methoxybenzylthio) phenylacetate

A mixture of methyl 3-(4-methoxybenzylthio)-4-nitrophenylacetate(1.2g), methanol(25mL), tetrahydrofuran(25mL), water(10mL), ammonium chloride(0.2g) and iron powder(1g) was stirred at reflux for two hours. The mixture was cooled, diluted with water and ethyl acetate and filtered and the organic phase was separated, dried and evaporated to dryness to give the product(1.05g)[m/e318,MH+].

23iii) Preparation of Methyl 3-(4-methoxybenzylthio)-4-(phenylthioureido) phenylacetate

A mixture of methyl 4-amino-3-(4-methoxybenzylthio) phenylacetate(0.8g), acetonitrile(5mL) and phenylisothiocyanate(0.34g) was stirred at 60°C for 18hr. The mixture was evaporated to dryness and the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product (0.42g), [m/e453,MH+].

23iv) Preparation of 2-Anilino-6-methoxycarbonylmethyl benzothiazole

A mixture of methyl 3-(4-methoxybenzylthio)-4-(phenylthioureido) phenylacetate(0.42g), trifluoroacetic acid(5mL) and yellow mercuric oxide(0.3g) was stirred at 70°C for 1hr, cooled to ambient temperature and treated with water and ethyl acetate. The organic phase was separated and washed successively with water, aqueous sodium hydrogen carbonate and brine. The extract was dried evaporated to dryness and the residue was purified

by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product. (0.25g), [m/e299,MH+].

Method 24 - Preparation of 2-(Pyrid-3-ylamino)-6-{3-[3-carboxypropoxy] anilinocarbonyl methyl}benzothiazole

6-Ethoxycarbonylmethyl-2-(pyrid-3-ylamino)benzothiazole was hydrolysed by the process described in Method Ia to give 6-carboxymethyl-2-(pyrid-3-ylamino)benzothiazole [m/e286,MH-] which was used in the coupling process A(i) to give, after hydrolysis, 2-(pyrid-3-ylamino)-6-{3-[3-carboxypropoxy]anilinocarbonylmethyl}benzothiazole (example 126).

24i) Preparation of N-4-ethoxycarbonylphenyl-N'-pyridylthiourea

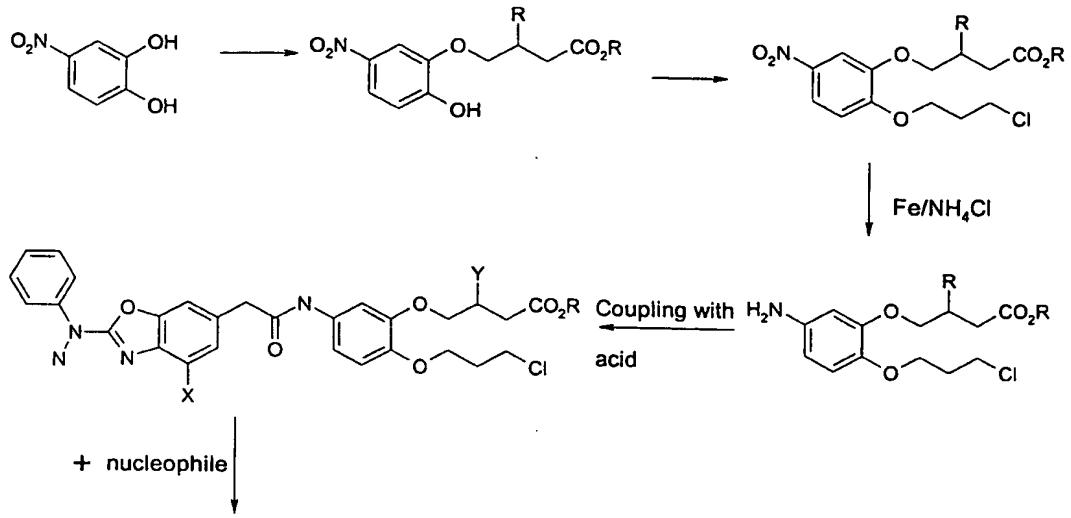
A mixture of ethyl 4-aminophenylacetate(0.9g), acetonitrile(3mL) and 3- pyridyl isothiocyanate was stirred at 60°C for 1h. The mixture was evaporated to dryness and the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate and hexane to give the product(1.37g), [m/e316,MH+].

24ii) Preparation of 6-Ethoxycarbonylmethyl-2-(pyrid-3-ylamino)benzothiazole

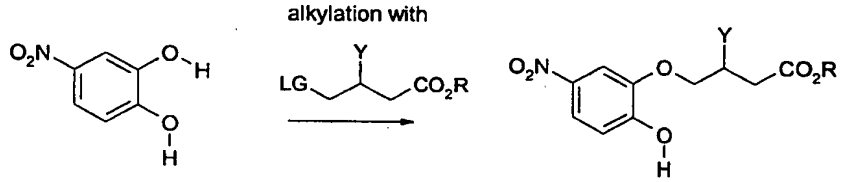
A solution of bromine(0.16g) in dichloromethane(2mL) was added dropwise over 5 minutes to a stirred solution of N-4-ethoxycarbonylphenyl-N'-pyridylthiourea(0.31g) in trifluoroacetic acid(2mL) and the mixture was stirred at ambient temperature for 2h. The stirred mixture was made basic with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extract was dried and evaporated to dryness and the residue was triturated with a small volume of dichloromethane. The insoluble solid was collected to give the product(0.12g), [m/e314,MH+].

Method 25

The general reaction scheme is given below

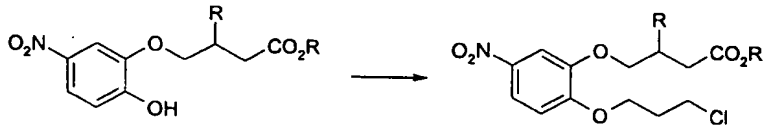


i) Dianion alkylation of nitrocatechol



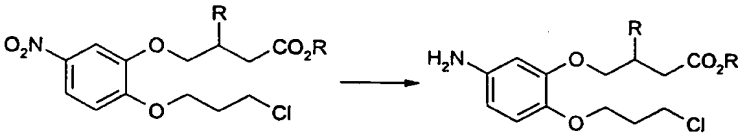
Sodium hydride (5.2g of a 60% suspension in oil; 129mmol) was suspended in DMF (50mL) and cooled to 0° C. 4-Nitrocatechol (10g; 64.5mmol) in DMF (50mL) was slowly added. The purple solution that formed was stirred for 0.5hr and then electrophile (selected from methyl 4-bromobutyrate or methyl 3-methyl-4-bromobutyrate (64.5mmol)) was added. The reaction mixture was very viscous for about 1h but after this time it became quite fluid. The mixture was stirred for 24h by which time it had become red in colour. The reaction mixture was quenched by careful addition of water and then acidified with 2N hydrochloric acid causing the mixture to turn pale yellow. The mixture was extracted with ethyl acetate (x2) and the combined extracts washed with brine (x2), saturated, aqueous sodium bicarbonate, brine, dried and concentrated under reduced pressure. The yellow sticky solid was washed with hexane to remove mineral oil and gave nitrophenol (15g, 67%) as a pale yellow solid.

ii) **Alkylation of phenol**



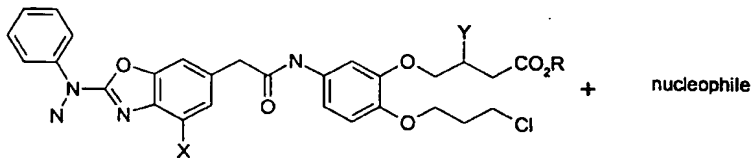
Nitro phenol (0.62mmol) and 1-bromo-3-chloropropane (0.74mmol) were dissolved in DMF (2mL) and potassium carbonate (254mg; 1.84mmol) was added. The reaction mixture was heated at 80°C for 4h. After cooling, the reaction mixture was diluted with ethyl acetate and washed with brine (x3), dried ($MgSO_4$) and concentrated under reduced pressure.

iii) **Reduction of nitro group**



The nitrobenzene derivative (8.39mmol), iron powder (2.8g; 50.3mmol) and ammonium chloride (0.3g; 5.87mmol) were heated at reflux in ethanol (56mL) and water (18mL) for 1h. The iron was filtered off and the filtrate concentrated under reduced pressure. The residue was taken up in dichloromethane (DCM) washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the aniline as a brown oil.

The corresponding aniline was coupled to the anilinobenzoxazole acetic acid according to procedure in table 1, column "penultimate stage" to give the general intermediate below:

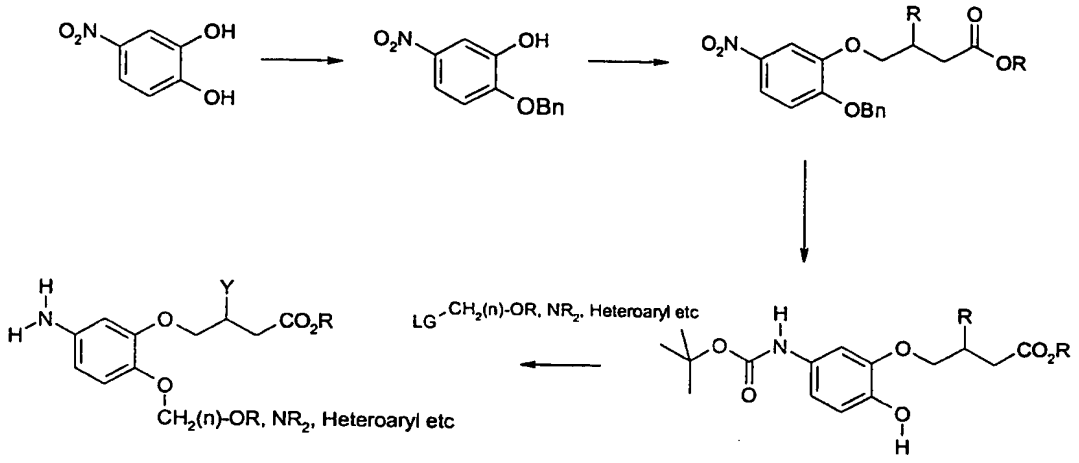


The propoxychloride ester (0.22mmol) and nitrogenous nucleophile (selected from piperidine; bis(2methoxyethyl)amine; piperazine; N-methylpiperazine; morpholine;

2-methoxyethyamine; dimethylamine; pyrrolidine; imidazole; 0.44mmol) were heated together in N,N-dimethylacetamide (1mL) at 80°C for 5.5h. The reaction mixture was cooled, diluted with ethyl acetate and washed with brine (x3) and dried ($MgSO_4$). After concentrating under reduced pressure, the residue was chromatographed (5%MeOH/DCM -

10%MeOH/DCM - 20%MeOH/DCM) to give desired product esters, which were hydrolysed according to the general procedure in table 1, column "final stage".

Method 26A and 26B

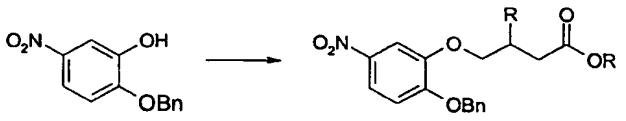


i) **Benzylation of nitrocatechol:**

Sodium hydride (1.4g of a 60% suspension in mineral oil; 34.6mmol) was suspended in DMF (15mL) cooled to ca. 0°C. 4-Nitrocatechol (5.4g; 34.8mmol) in DMF (15 mL) was slowly added giving a dark purple coloured solution. After 0.5h benzyl bromide (4.1 mL; 34.8mmol) was added and the reaction mixture stirred for 24h at room temperature. The reaction mixture was carefully quenched by the dropwise addition of water and most of the DMF removed under reduced pressure. This caused sodium bromide to precipitate. The residue was taken up in ethyl acetate and washed with brine (3 times), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed (DCM) and the product containing fractions shaken with 2M NaOH giving a red aqueous layer from which an orange solid precipitated. This was redissolved by the addition of water. The aqueous layer was separated and acidified with 2M aqueous hydrochloric acid and extracted with DCM. The extracts were

dried and concentrated under reduced pressure to give the product (4.1g, 48%) as a yellow crystalline solid.

ii) (a) Alkylation of phenol:

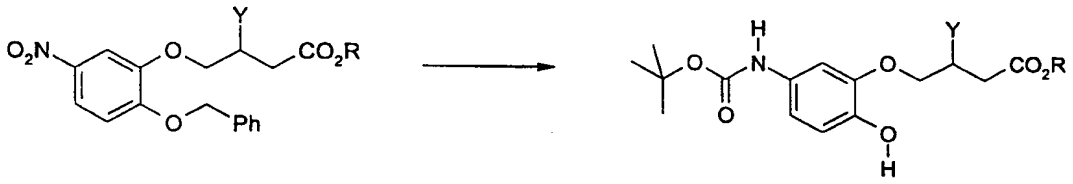


Phenol (16.7mmol), appropriate electrophile (selected from methyl 4-bromobutyrate; methyl 3-methyl-4-bromobutyrate; ethyl S-3-methyl-4-bromobutyrate; 18.4mmol) and potassium carbonate (6.9g; 50.1mmol) were heated together in DMF (25 mL) at 80°C over night. A small amount of water was added to dissolve the solid and the DMF removed under reduced pressure. The residue was taken-up in ethyl acetate and washed with brine (3 times), dried ($MgSO_4$) and concentrated under reduced pressure to give desired ester.

ii) (b) Alkylation of phenol

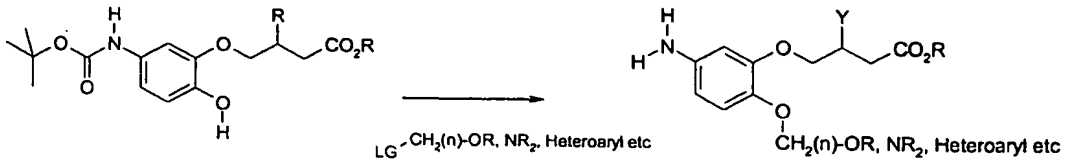
The above phenol can also be alkylated according to Method 4a (Mitsunobu Reaction).

iii) De-benzylation/hydrogenation and Boc protection



Nitro ester (16.2mmol) was added to ethanol (75mL) and the system purged with argon gas. 10% Palladium on carbon (10% by mass) was added and the reaction mixture stirred under a atmosphere of hydrogen for 2.5h. The reaction mixture was filtered and concentrated under reduced pressure to give a the aminophenol as a pale brown solid. The aminophenol was immediately dissolved in THF (50mL) and di-tert-butyl dicarbonate (3.93g; 18.0mmol) added. The mixture was heated under reflux for 1.5h and then cooled and concentrated under reduced pressure. The resulting solid was suspended in isohexane and sonicated for a few minutes before being filtered off and washed with isohexane:diethylether (1:1) to give N-Boc-anilino phenol as a pale pink solid.

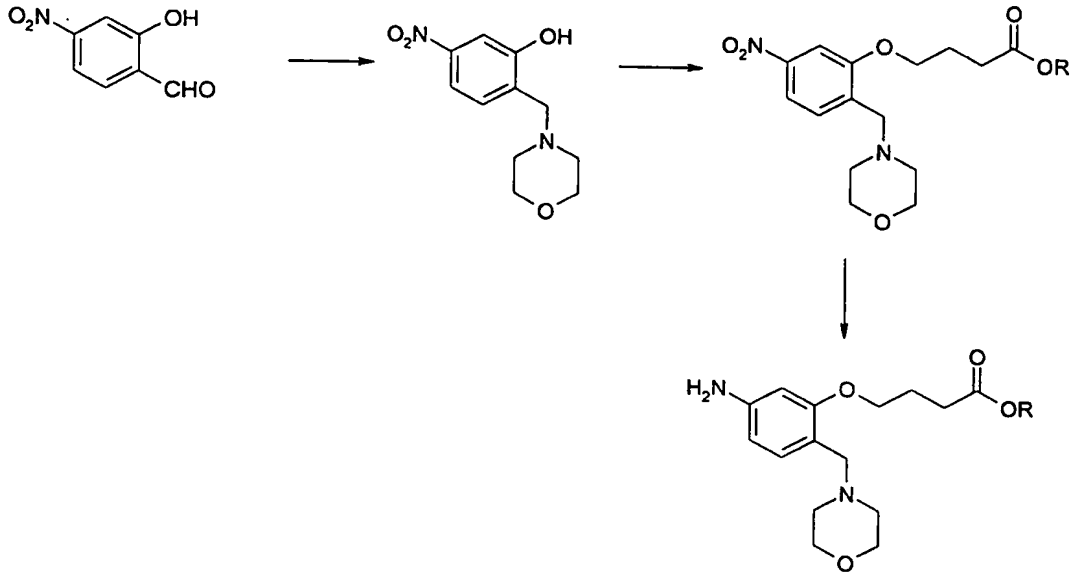
iv) **Alkylation and deprotection**



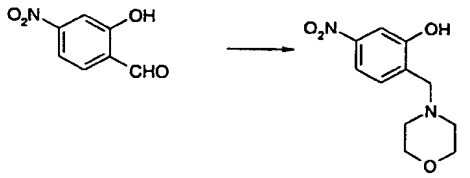
N-Boc-anilino phenol (0.62mmol) and appropriate electrophile (selected from 2-chloroethyl methyl ether; N-(2-chloro ethyl) piperidine hydrochloride; N-(2-chloroethyl) morpholine hydrochloride; 2-chloromethylpyridine hydrochloride; 3-chloromethylpyridine hydrochloride; 4-chloro methyl pyridine hydrochloride; N-(2-chloroethyl)pyrrolidine hydrochloride; 2-dimethylamino ethyl hydrochloride; and 1-(2-chloroethyl)-imidazole hydrochloride (0.74mmol)) were dissolved in DMF (2mL) and potassium carbonate (254mg; 1.84mmol) was added. The reaction mixture was heated at 80°C for 4h. After cooling, the reaction mixture was diluted with ethyl acetate and washed with brine (x3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed (DCM - 1%MeOH/DCM - 2%MeOH/DCM) to give the desired N-Boc-anilino phenol ether. The N-Boc-anilino phenol ether (0.34mmol) was dissolved in 4M hydrogen chloride in dioxane (5mL) and the mixture stirred at room temperature for 0.5h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in DCM, washed with saturated, aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure to give aniline.

Those compounds produced by alkylation method 26ii)(b)described above suffered loss of the tert-butyl ester under treatment with 4M hydrogen chloride. These were re-esterified in the following manner: Methanol (2ml) was cooled to 0°C and to it was added $SOCl_2$ (0.39mmol) and a methanolic solution (1ml) of the acid (0.36mmol). The mixture was allowed to warm to room temperature with stirring. The solvent was removed under reduced pressure and the residue was purified using an NH_2 isolute column eluted with methanol. This aniline was coupled to the anilinobenzoxazole acetic acid according to procedure in table 1, column "penultimate stage" to give desired product esters, which were hydrolysed according to the general procedure in table 1, column "final stage".

Method 27

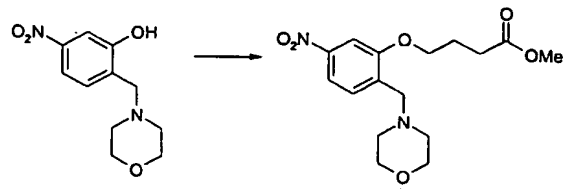


i) Reductive amination of 2-hydroxy-4-nitrobenzaldehyde.



Molecular sieve (type 3A 120mg.) was added to a solution of 2-hydroxy-4-nitrobenzaldehyde (0.2g,1.2mmole) in dry methanol followed by morpholine (0.31ml,3.6mmole) and glacial acetic acid (1.0ml). Finally sodium cyanoborohydride (0.21g,2.4mmole) was added portionwise with stirring over 5 minutes at ambient temperature and stirring was continued for 18 hours. After filtering off the insoluble material the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane and washed twice with water, after drying (magnesium sulphate) the solvent was evaporated to yield a gum (0.15g,53%) which was used without further purification ; ms239$(M+H)^+$.

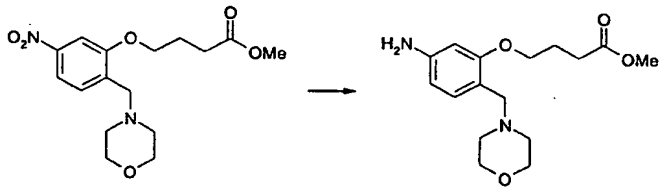
ii) Alkylation of phenol



The above oil (0.15g,0.63mmole) was dissolved in DMF (10ml). Methyl 4-bromobutyrate (0.13g,0.7mmole) and potassium carbonate (0.1g,0.7mmole) were added and the resultant mixture was heated at 80° for 6 hours. After filtration, the solvent was evaporated. The residue was dissolved in dichloromethane, washed twice with water, dried (magnesium sulphate) and evaporated in vacuo to yield an oil. The oil was chromatographed (Varian megabondelut 10g silica) using a gradient of 100% dichloromethane to 20% ethyl acetate/dichloromethane to give the desired ether (0.1g,49%).

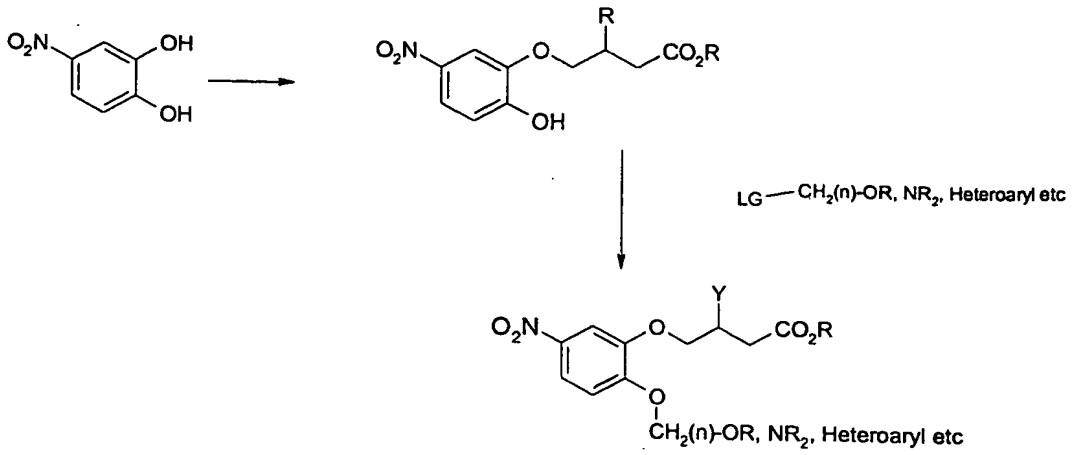
nmr: 2.0(m,2H), 2.25(m,2H), 2.4(m,4H), 3.5(s,3H), 3.55(m,6H), 4.1(m,2H), 7.6(m,1H), 7.7(m,1H), 7.8(m,1H):ms 339(M+H)

iii) Reduction of nitrobenzene to aniline



The nitro benzene was reduced to the aniline using ammonium formate reduction under Pd (10% on Carbon) catalysis in ethanol at room temperature, according to the procedure described in Tetrahedron Lett. 1994, 171-4. : ms 309(M+H).

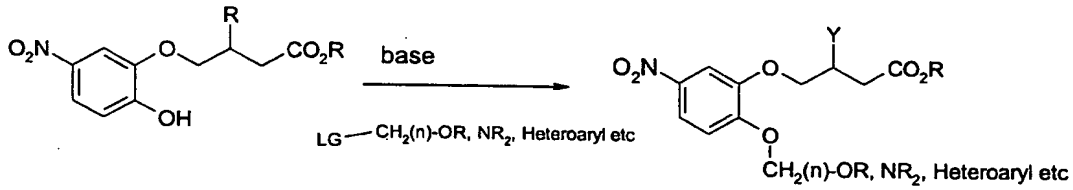
Method 28



i) Dianion alkylation of nitrocatechol

This was carried according to the procedure described in method 25.

ii) Alkylation of phenol



Nitro phenol (0.62mmol) and electrophile (selected from 1-(2-chloroethyl)-imidazole hydrochloride, N-(2-chloroethyl) piperidine hydrochloride, N-(2-chloroethyl)pyrrolidine hydrochloride, 4-chloromethylpyridine hydrochloride and 2-chloroethyl-bis-(2-methoxy-ethyl)-amine (0.74mmol)) were dissolved in DMF (2mL) and potassium carbonate (254mg; 1.84mmol) was added. The reaction mixture was heated at 80°C for 4h. After cooling, the reaction mixture was diluted with ethyl acetate and washed with brine (x3), dried ($MgSO_4$) and concentrated under reduced pressure.

Method 29 - Preparation of Methyl 3-(S-leucylamino)-3-[–benzo[1,3]dioxol-5-yl)phenyl]propanoate

Methyl 3-(1,3-benzodioxol-5-yl)-3-({2-[tert-butoxycarbonyl)amino]4-methylpentanoyl} amino)propanoate (10g) was treated with 90% TFA in water(100mL). The

mixture was stirred for 30 min and the TFA and water were then removed by evaporation. The residue was purified by preparative HPLC on a C18 silica column eluting with acetonitrile/water/0.1% TFA to give a gummy solid on evaporation of appropriate fractions. This was dissolved in ethyl acetate (50mL) and washed twice with saturated sodium bicarbonate solution(10mL), once with saturated brine(10mL), dried ($MgSO_4$) and evaporated to give the product.

1H NMR (DMSO-d6, 300 MHz, ppm) : 0.8(6H, m), 1.3-1.5(2H,m), 1.5-1.6(1H,m), 2.7(2H,m), 3.3-3.4(1H,m), 3.5(3H,s), 4.9-5.3(2H,b), 5.1-5.2(1H, m), 6.0(2H,s), 6.7-6.9(3H,m), 8.4-8.5(1H,d), : m/Z 337 (M+H).

29i) Preparation of Methyl 3-(1,3-benzodioxol-5-yl)-3-({2-[tert-butoxycarbonyl)amino]4-methylpentanoyl}amino)propanoate

HOBT (255mg) was added to a solution of N-(t-butoxycarbonyl)leucine (297mg) in DMF (5mL), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (273mg) and the solution stirred for 15 min. Methyl 3-amino-3-(3,4-methylenedioxyphenyl) propionate (185mg) (prepared according to the method described in WO96/22966 (Biogen) at pages 52 to 55 and incorporated herein by reference) was dissolved in DMF (5mL) and triethylamine (140µl). The resultant solution added to the solution of the N-(t-butoxycarbonyl)leucine activated ester followed by diisopropylethylamine (100µl). The mixture was stirred overnight at ambient temperature. The mixture was then added to ethyl acetate(30mL), washed with water (2x5mL), 5% citric acid (5mL), water (5mL), saturated sodium bicarbonate solution (5mL), water (5mL), saturated brine (5mL), dried ($MgSO_4$) and evaporated to give the product.

1H NMR (DMSO-d6, 300 MHz, ppm) : 0.9(6H, m), 1.3-1.5(3H,m), 2.7(2H,m), 3.5(3H,s), 4.8-4.9(1H,m), 5.1-5.2(1H, m), 5.9(2H,s), 6.7-6.9(4H,m), 8.2(1h,d), : m/Z 437 (M+H) .

Method 30 - Preparation of Methyl 3-(S-methionylamino)-3-[–benzo[1,3]dioxol-5-yl)phenyl]propanoate

This was prepared by method 29 but using N -(t-butoxycarbonyl)methionine in place of N -(t-butoxycarbonyl)leucine.

1H NMR (DMSO-d6, 300 MHz, ppm) : 1.8-1.9(2H,m), 2.0 (3H,s), 2.2-2.4(2H,m), 2.7-2.9(2H,m), 3.5(3H,s), 3.7(1H,t), 5.1(1H,b), 6.0(2H,s), 6.7-6.9(3H,m), 7.1-7.4(2H,b), 8.8(1H,d): m/Z 355 (M+H) .

Example 140

The compounds of the invention or pharmaceutically acceptable salts thereof may be formulated into tablets together with, for example, lactose Ph.Eur, Croscarmellose sodium, maize starch paste (5% w/v paste) and magnesium stearate for therapeutic or prophylactic use in humans. The tablets may be prepared by conventional procedures well known in the pharmaceutical art and may be film coated with typical coating materials such as hydroxypropylmethylcellulose.

In Vitro and In Vivo Assays

The following abbreviations are used. Suitable sources of materials are listed below.

MOLT-4 cells - human T-lymphoblastic leukaemia cells (European Collection of Animal Cell Cultures, Porton Down)

Fibronectin - purified from human plasma by gelatin-sepharose affinity chromatography according to the methods described in E.Nengvall, E.Ruoslahti, Int. J. Cancer, 1977, 20, pages 1-5 and J. Forsyth et al, Methods in Enzymology, 1992, 215, pages 311-316).

RPMI 1640 - cell culture medium. (Life technologies, Paisley UK).

PBS - Dulbecco's phosphate buffered saline (Life Technologies).

BSA - Bovine serum albumin, fraction V (ICN, Thame, UK).

CFA - Complete Freund's Adjuvant (Life Technologies).

In the following assays and models references to compound(s) refers to the compounds of formula (I) and (II) according to the present invention.

1.1 In vitro assay

1.1.1 MOLT-4 cell/ Fibronectin adhesion assay.

The MOLT-4 cell /fibronectin adhesion assay was used to investigate the interaction of the integrin α_4-$\beta_1$expressed on the MOLT-4 cell membrane with fibronectin. Polystyrene 96 well plates were coated overnight at 4°C with fibronectin, 100 µl of 10 µg/ml in PBS. Non-specific adhesion sites were blocked by adding 100 µl BSA, 20 mg/ml. After incubating

for 1 h at room temperature, the solutions were aspirated. MOLT-4 cells suspended in serum-free RPMI-1640 medium 2E6 cells/ml (50 µl) and solutions of compound diluted in the same medium (50 µl) were added to each well. After incubation for 2 h at 37°C in a humidified atmosphere of 5% (v/v) CO_2, non-adherent cells were removed by gentle shaking followed by vacuum aspiration. Adherent cells were quantified by a colorimetric acid phosphatase assay. To each well was added 100 µl p-nitrophenyl phosphate (6 mg/ml) in 50 mM sodium acetate buffer, pH 5.0, containing 1% Triton X-100. After incubation for 1 h at 37°C, 50 µl sodium hydroxide (1M) was added to each well and the absorbance 405 nm was measured on a microplate spectrophotometer.Compounds which inhibited adhesion gave a lower absorbance reading. Standard, control and test conditions were assayed in triplicate. Percentage inhibition was calculated with respect to total (no inhibitor) and non-specific (no fibronectin) standards on each plate.

1.2 In-vivo Inflammation Models

Activity of a compound can be tested in the following models.

1.2.1 Ovalbumin Delayed type Hypersensitivity in mice

Balb/c female mice (20-25g) are immunised on the flank with an 1:1 (v/v) emulsion of ovalbumin (2 mg/ml) with CFA. Seven days later the mice are challenged by subplantar injection of 1% heat aggregated ovalbumin in saline (30 µl) into the right hind foot pad. Swelling of the foot develops over a 24 hour period following which foot pad thickness is measured and compared with the thickness of the contralateral uninjected foot. The percentage increase in foot pad thickness is calculated. Compounds are dosed orally by gavage to groups of 5 mice at doses ranging from 0.001 mg/kg to 100 mg/kg. Inhibition of the inflammatory response is calculated comparing vehicle treated animals and compound treated groups.

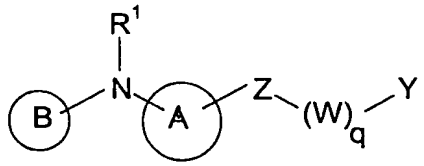
1.2.2. Collagen-induced arthritis in mice

DBA/1 male mice are immunised with 0.1ml of an emulsion prepared from equal volumes of bovine collagen type II in 0.05M acetic acid (2 mg/ml) and CFA. This mixture is injected at the base of the tail. Twenty days later compounds are dosed orally by gavage at

doses ranging from 0.001mg/kg/day to 100 mg/kg/day. On the day following the first dose, each animal receives an intra-peritoneal booster injection of 0.1ml of collagen type II in acetic acid. The mice are assessed for the incidence and severity of arthritis in all four limbs for up to 28 days. Inhibition of arthritis is calculated by comparing vehicle treated and compound treated mice.

CLAIMS

1. A compound of formula (I)



(I)

wherein:

A is a bicyclic heteroaryl, optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, halogeno, nitro, cyano, amino trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to the nitrogen via a ring carbon atom in one ring and to the group Z by a ring carbon atom in the second ring;

B is aryl or a mono or bicyclic heteroaryl, each of which can be optionally subsitituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, phenoxy, cyano, nitro, amino, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to NR^1 through a ring carbon atom;

Z is -$X(CR^aR^b)_aCO$, -NH, -CO or the group -X-$(CH_2)_bCONH(CH_2)_cNH$ where X is oxygen, sulphur, amino, alkylamino or a direct bond, R^a and R^b are independently hydrogen or C_{1-4} alkyl, a is an integer from 1 to 4, b is 1 or 2 and c is from 2 to 5, and;

W is -$NHCH(R^w)CO$- or $OC(R^w)CHNH$ where R^w is -$CH_2CH(CH_3)_2$

$-CH_2CH_2S(CH_3)$ or $CH_2CH_2S(O_2)(CH_3)$;

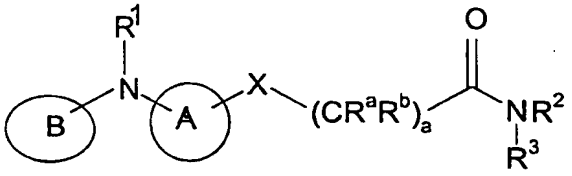
q is 0 or 1 and when q is 0 Z is linked to the group Y by the formation of an amide bond between Z and Y, and when q is 1 Z is linked to the group W by the formation of an amide bond between Z and W and W is linked to the group Y by the formation of an amide bond between W and Y;

Y is a fragment derived from the C-terminus of a compound which inhibits the interaction between the integrin $\alpha_{IIb}\beta_3$ and its ligand fibrinogen;

R^1 is hydrogen, C_{1-5} alkyl, C_{1-3} alkanoyl or C_{1-3} alkoxycarbonyl;

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

2. A compound of formula (II)



(II)

wherein:

A is a bicyclic heteroaryl, optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, halogeno, nitro, cyano, amino trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to the nitrogen via a ring carbon atom in one ring and to the group Z by a ring carbon atom in the second ring;

B is aryl or a mono or bicyclic heteroaryl, each of which can be optionally subsitituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{1-4} alkylsulphonyl, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, carboxy, carbamoyl, C_{2-6} alkenyloxy, C_{2-6}alkynyloxy, di-[(C_{1-6})alkyl]amino, C_{2-6}alkanoylamino, N-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxylcarbonyl, phenoxy, cyano, nitro, amino, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p

is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen or C_{1-6} alkyl, linked to NR^1 through a ring carbon atom;

R^a and R^b are independently hydrogen or C_{1-4} alkyl;

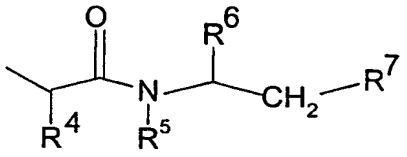
a is an integer from 1 to 4;

X is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

R^1 is hydrogen, C_{1-5} alkyl, C_{1-3} alkanoyl or C_{1-3} alkoxycarbonyl;

R^3 is hydrogen or C_{1-5} alkyl;

R^2 is selected from a group of formula (III) or (IV),



(III)

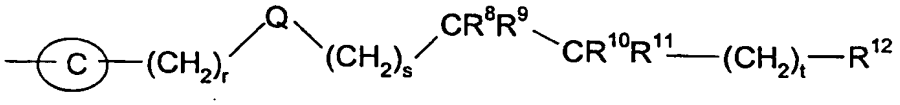
where

R^4 is selected from C_{1-6} alkyl, C_{1-6}alkoxy(C_{1-6})alkyl, C_{1-6}alkylS(C_{1-6})alkyl and C_{1-6}alkylS(O_2)(C_{1-6})alkyl;

R^5 is hydrogen or C_{1-5} alkyl;

R^6 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, and aryl optionally substituted by at least one substituent selected from C_{1-4} alkoxy, C_{1-6} alkyl, cyano, halogeno, and trifluoromethyl; and

R^7 is an acidic functional group;



(IV)

where

C is aryl, a monocyclic heteroaryl linked through ring carbon atoms, a bicyclic heteroaryl linked to nitrogen by a ring carbon in one ring and to the group $(CH_2)_r$ or, where r is zero, Q by a ring carbon in the second ring, the aryl and mono and bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-}

$_6$alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl; and a substituent of formula (V)

$$U - (CH_2)_d - V - T \qquad (V)$$

wherein U is selected from oxygen, sulphur, a direct bond or -CH_2O-, V is selected from nitrogen, oxygen, sulphur or a direct bond, d is zero or a number from 1 to 4, and T is selected from R^c or, when V is nitrogen, R^cR^d,where R^c and R^d are independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxy(C_{1-6})alkyl or aryl; or a heterocycle containing up to three heteroatoms selected from nitrogen, oxygen and sulphur, optionally substituted with one or more substituents selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-4} alkylsulphonyl, nitro, cyano, halogeno, trifluoromethyl, trifluoromethoxy, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl, and linked to V through a ring carbon or nitrogen and with the proviso that when T is a heterocycle linked to V through a ring nitrogen then V is a direct bond;

Q is selected from a direct bond, methylene, oxygen, carbonyl, -C(OH)(H)- or Q together with the group $(CH_2)_s$ or CR^8R^9, when s is zero, form a C_2 alkenyl or C_2 alkynyl;

R^8 to R^{10} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heterocycle, the aryl and heterocycle optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{1-4}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl, or two of R^8 to R^{10} can be taken together to form phenyl or a 3-7 membered heterocycle;

R^{11} is selected from hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, hydroxy, amido, heterocycle and aryl, the heterocycle, and aryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{1-4}alkanoyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and

-$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{12} is an acidic functional group;

r is zero or 1;

s is zero, 1 or 2;

t is zero or a number from 1 to 3;

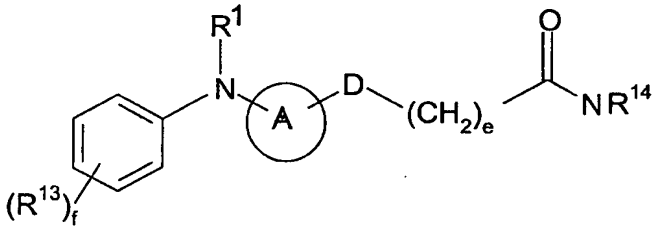
or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

3. A compound according to claim 1

wherein B is a phenyl optionally substituted with up to five substituents independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, are - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two substituents can be taken together to form a 5-7 membered ring; and when Z is -X-$(R^aR^b)_aCO$- then R^a and R^b are both hydrogen

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

4. A compound according to claim 2 having the formula (VI)



(VI)

wherein:

A, and R^1 are as defined in claim 2;

each R^{13} is independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form a 5-7 membered ring;

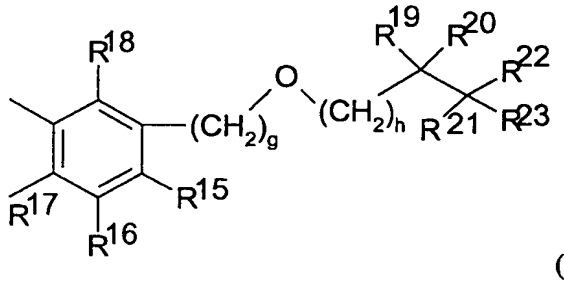
D is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

e is an integer from 1 to 4;

f is zero or an integer from 1 to 5;

R^{14} is selected from a group of formula (III), as hereinbefore defined where R^4 is C_{1-6} alkyl, C_{1-6}alkoxy(C_{1-6})alkyl, and C_{1-6}alkylS(C_{1-6})alkyl;

or from a group of formula (VII)



(VII)

where

R^{15} to R^{18} are each independently hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2 - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

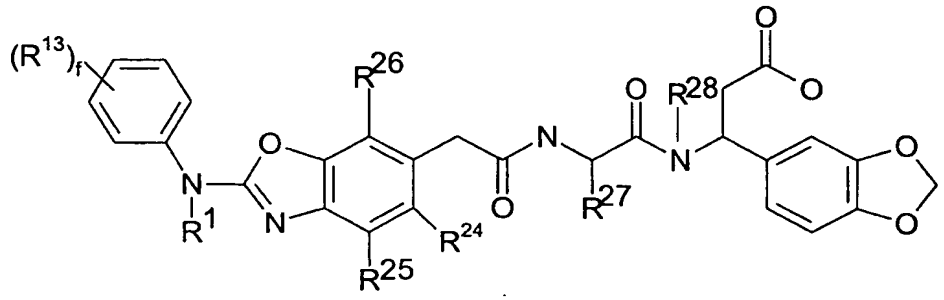
R^{19} to R^{22} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heteroaryl containing up to 2 heteroatoms chosen from oxygen, sulphur and nitrogen, the aryl and heteroaryl optionally substituted with one or more substituents selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6}, or two of R^{19} to R^{22} can be taken together to form phenyl or 3 to 7 membered heterocycle;

R^{23} is an acidic functional group; and

g and h are each independently 0 or 1;

or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof.

5. A compound according to claim 2 having the formula (VIII)



(VIII)

wherein:

R^1 is as defined in claim 2;

each R^{13} is independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form a 5-7 membered ring;

f is zero or an integer from 1 to 5;

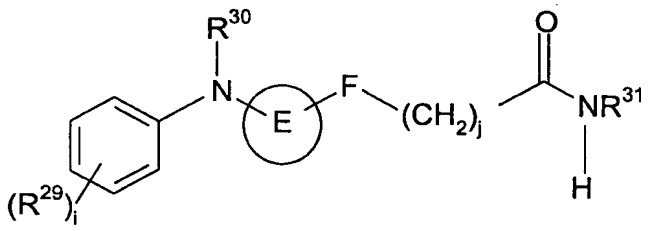
R^{24} to R^{26} are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkanoyl or halogeno;

R^{27} is $-CH_2CH(CH_3)(CH_3)$ or $-CH_2CH_2SCH_3$; and

R^{28} is hydrogen or C_{1-5} alkyl;

or a pharmaceutically acceptable salt or in vivo hydrolysable derivative thereof.

6. A compound according to claim 2 having the formula (IX)



(IX)

wherein:

each R^{29} is independently selected from C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, nitro, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently hydrogen and C_{1-6} alkyl, or two adjacent substituents can be taken together to form phenyl or a 5-7 membered heterocycle;

R^{30} is hydrogen, C_1-$_5$ alkyl, C_1-$_3$ alkanoyl or C_1-$_3$ alkoxycarbonyl;

E is a bicyclic heteroaryl optionally substituted with one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkanoyl, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, halogeno, nitro, cyano, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are

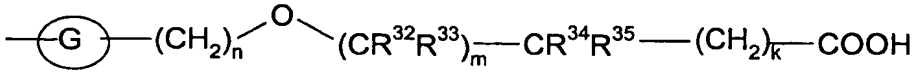
independently hydrogen and C_{1-6} alkyl, and is linked to the nitrogen via a ring carbon atom in one ring and to the group F by a ring carbon atom in the second ring;

F is a direct bond, oxygen, sulphur, amino or C_{1-4}alkylamino;

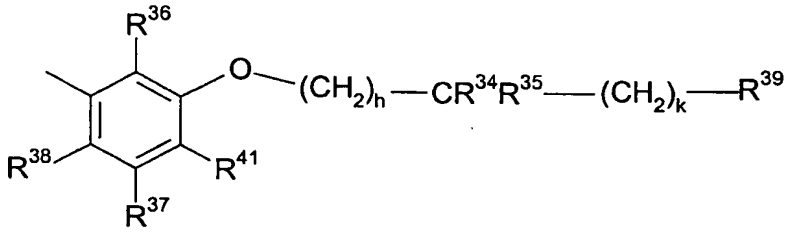
i is zero or an integer from 1 to 4;

j is an integer from 1 to 4;

R^{31} is selected from a group of formula (X) or (XI)



(X)



(XI)

where

R^{41} is a group of formula U - $(CH_2)_d$ - V -T as defined in claim 2;

G is aryl, a monocyclic heteroaryl linked through ring carbon atoms, a bicyclic heteroaryl linked to nitrogen by a ring carbon in one ring and to the group $(CH_2)_n$ or oxygen by a ring carbon in the second ring, the aryl and mono and bicyclic heteroaryl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, - CO_2R^e, and -$CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{32} to R^{34} are each independently selected from hydrogen, C_{1-6} alkyl, aryl and heterocycle, the aryl and heterocycle optionally substituted with one or more substituents independently selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, -CO_2R^e and -$CONR^eR^f$, where R^e and R^f are

independently selected from hydrogen and C_{1-6} alkyl or two of R^{32} to R^{34} can be taken together to form phenyl or a 3-7 membered heterocycle;

R^{35} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6}alkenyl, 1,3-benzodioxol-5-yl, an ester group, amido, heterocycle and aryl, the heterocycle, and aryl optionally substituted with one or more substituents independently selected from nitro, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{1-4}alkylC_{1-6}alkyoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2, $-CO_2R^e$ and $-CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{36} to R^{38} are each independently hydrogen, C_{1-6} alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-6} alkylamino, C_{1-4}alkoxylC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, nitro, cyano, halogeno, trifluoromethyl, hydroxy, $(CH_2)_pOH$ where p is 1 or 2 - CO_2R^e, and - $CONR^eR^f$, where R^e and R^f are independently selected from hydrogen and C_{1-6} alkyl;

R^{39} is an acidic functional group;

h and n are zero or 1;

m is zero, 1 or 2;

k is zero or a number from 1 to 3;

or a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable derivative thereof.

7. A compound of formula (II) according to claim 2 where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as defined in claim 2, B is phenyl, optionally substituted as defined in claim 2, A and B are linked together as shown in figure (1),

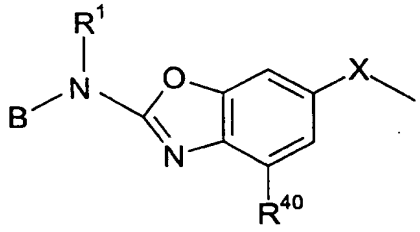


figure (1)

X is a direct bond or oxygen and R^1 is hydrogen or C_{1-2} alkyl; and

(i) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, C_{1-6}alkyl$S(C_{1-6})$alkyl or C_{1-6}alkyl$S(O_2)(C_{1-6})$alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy;

(ii) R^3 is methyl, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(iii) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, C_{1-6}alkylS(C_{1-6})alkyl or C_{1-6}alkylS(O_2)(C_{1-6})alkyl, R^5 is hydrogen, R^6 is C_{1-6} alkyl and R^7 is carboxy;

(iv) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is -COOR", where R" is 2,4-dimethyl-pent-3-yl or 2,2-dimethylaminoethyl, isopropoxyphenyl; $-C_2H_4N(CH_3)_2$ and R^7 is carboxy;

(v) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as defined in claim 2;

(vi) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl substituted with one or more substituents selected from methoxy, cyano, halogeno, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as defined in claim 2;

(vii) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl or a C_{2-3} alkenyl, R^{12} is carboxy, r and s are both zero and t is 1;

(viii) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl substituted with a C_{1-4} alkoxy, C_{1-4} alkyl, halogeno, or trifluoromethyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl or a C_2 alkenyl, R^{12} is carboxy, r and s are both zero and t is 1;

(ix) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl optionally substituted with C_{1-4} alkoxyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is a nitrogen containing heterocycle, R^{12} is carboxy, r and s are both zero and t is 1;

(x) R^3 is hydrogen and R^2 is a group of formula (IV), where C is phenyl, optionally substituted with C_{1-4} alkoxyl, Q is oxygen, R^8 to R^{10} are all hydrogen, R^{11} is phenyl substituted with a C_3 alkoxy, R^{12} is carboxy, r and s are both zero and t is 1;

(xi) R^3 is methyl and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as defined in claim 2; or

(xii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r is zero, s and t are both one and R^8 to R^{11} are all hydrogen;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

8. A compound of formula (II) according to claim 2 where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as defined in claim 2, B is phenyl, optionally substituted as defined in claim 2, A and B are linked together as shown in figure (2)

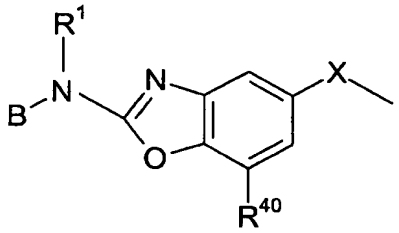


figure (2)

X is a direct bond and R^1 is hydrogen or C_{1-2} alkyl and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as defined in claim 2;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

9. A compounds of formula (II) according to claim 2

where R^a and R^b are both hydrogen, a is 1, A is benzimidazolyl, optionally substituted as defined in claim 2, B is phenyl, optionally substituted as defined in claim 2, X is a direct bond and R^1 is hydrogen or C_{1-2} alkyl; and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy or

(ii) R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are as defined in claim 2;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

10. A compounds of formula (II) where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as defined in claim 2, B is phenyl, optionally substituted as defined in claim 2, A and B are linked together as shown in figure (1), R^1 is hydrogen or C_{1-2} alkyl, X is a direct bond or oxygen, R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, r and s are both zero

i) R^8 to R^{10} are all hydrogen, R^{11} is 1,3-benzodioxol-5-yl, R^{12} is carboxy, t is 1 and Q is -C(OH)(H)-, carbonyl, methylene;

ii) R^{11} is 1,3-benzodioxol-5-yl, R^{12} is carboxy, t is 1 and Q together with the group CR^8R^9 form a C_2 alkenyl or C_2 alkynyl; or

iii) R^{11} is hydrogen, R^{12} is carboxy, t is 1 and Q together with the group CR^8R^9 form a C_2 alkenyl or C_2 alkynyl;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

11. A compound of formula (II) as claimed in claim 2 where R^a and R^b are both hydrogen, a is 1, A is benzoxazolyl, optionally substituted as defined in claim 2, B is naphthyl, pyridyl or N-oxidopyridyl optionally substituted as defined in claim 2, A and B are linked together as shown in figure (1), X is a direct bond or oxygen, R^1 is hydrogen or C_{1-2} alkyl; and

(i) R^3 is hydrogen, and R^2 is a group of formula (III) where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen, and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as defined in claim 2, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are all hydrogen;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

12. A compounds of formula (II) according to claim 2 where R^a and R^b are both hydrogen, a is 1, A is benzothiazolyl, as defined in claim 2, B is phenyl or pyridyl, both optionally substituted as defined in claim 2, A and B are linked together as shown in figure (3)

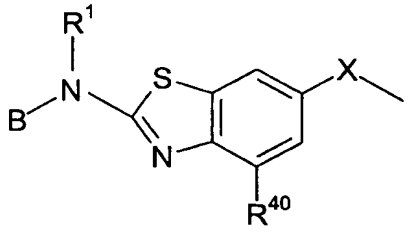


figure (3)

X is a direct bond or oxygen, and R^1 is hydrogen or C_{1-2} alkyl, and

(i) R^3 is hydrogen, and R^2 is a group of formula (III), where R^4 is C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy; or

(ii) R^3 is hydrogen, and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as defined in claim 2, Q is oxygen, R^{12} is carboxy, r and s are both zero, t is one and R^8 to R^{11} are all hydrogen;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

13. A compound of formula (IX) according to claim 6 where E is benzoxazolyl, optionally substituted as defined in claim 2, i is zero or 1, and is linked to the phenyl as shown in figure (1), F is a direct bond or oxygen, R^{30} is hydrogen or C_{1-2} alkyl, j is 1, R^{31} is a group of formula (XI), where R^{36} to R^{37} are as defined in claim 6, R^{39} is carboxy; and

i) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group C_{1-4}alkoxyC_{1-4}alkoxyl;

ii) h and k are both 1, R^{34} and R^{35} are both hydrogen, R^{41} is the group $O-(CH_2)_d-T$ where d is from 1 to 4, preferably 2 or 3, and T is a nitrogen containing heterocycle linked to oxygen through a ring nitrogen or ring carbon;

iii) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group $-O-(CH_2)_d-N-R^cR^d$, where d is 2 or 3, R^c and R^d are each independently $(CH_2)_2OCH_3$, C_{1-4} alkyl or hydrogen;

iv) h and k are both 1, R^{34} is hydrogen, R^{35} is a C_{1-4} alkyl or 1,3-benzodioxol-5-yl, and R^{41} is the group $-O-(CH_2)_d-T$ where d is from 1 to 4, and T is a nitrogen containing heterocycle linked to oxygen through a ring nitrogen and; or

v) h and k are both 1, R^{34} and R^{35} are both hydrogen and R^{41} is the group $-(CH_2)_d-T$ where d is 1 and T is morpholinyl;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

14. A compound of formula (II) according to claim 2 wherein a is 1, A is benzoxazolyl, optionally substituted as defined in claim 2, B is phenyl, optionally substituted as defined in claim 2, A and B are linked together as shown in figure (1), X is a direct bond and R^1 is hydrogen and

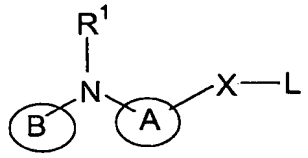
i) one or both of R^a and R^b are methyl, R^3 is hydrogen and R^2 is a group of formula (IV) where C is phenyl, optionally substituted as defined in claim 2, r and s are both zero, Q is oxygen, R^8 to R^{11} are hydrogen, t is 1 and R^{12} is carboxy; or

ii) one or both of R^a and R^b are methyl, R^3 is hydrogen and R^2 is a group of formula (III) where R^4 is a C_{1-6} alkyl, R^5 is hydrogen, R^6 is 1,3-benzodioxol-5-yl and R^7 is carboxy;

or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof in association with a pharmaceutically acceptable diluent or carrier.

16. A process for preparing a compound of formula (II), a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof which process comprises coupling together a compound of formula (XII)



(XII)

where L is a leaving group.

and an appropriate amine, where any functional group is optionally protected;

and thereafter, if necessary:

a) removing any protecting group; and

b) forming a pharmaceutically acceptable salt or in vivo hydrolysable derivative.

17. A method for inhibiting the interaction between VCAM-1 and/or fibronectin and the integrin receptor VLA-4 in mammals in need of such treatment which comprises administering to said warm-blooded mammals an effective amount of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof or a pharmaceutical composition according to claim 15.

18. A method according to claim 17 for treating multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease, psoriasis, atherosclerosis, transplant rejection, inflammatory bowel disease, insulin-dependent diabetes and glomerulonephritis.

19. The use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt or an in vivo hydrolysable derivative thereof in the production of a medicament for use in the treatment of a disease or condition mediated by the interaction between VCAM-1 and/or fibronectin and the integrin receptor VLA-4.